The American Journal of Medicine

November 1951

The American Journal of Medicine

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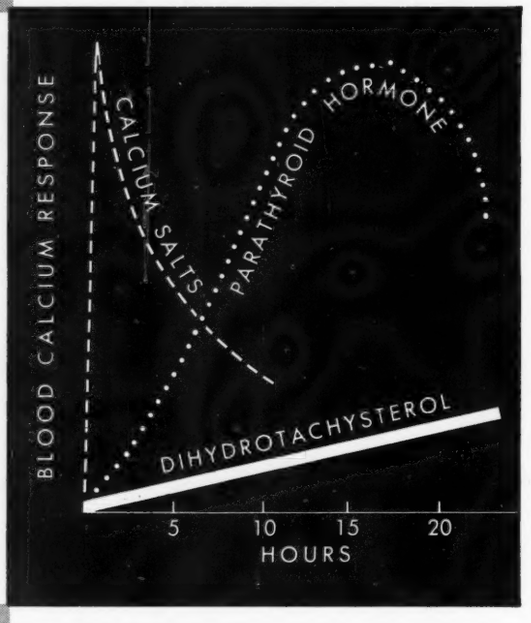

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*Grollman, A.: Essentials of Endocrinology. Philadelphia, J. B. Lippincott Co., 1947, 2d ed., p. 267,269.

Hytakerol, trademark reg. U. S. and Canada, brand of dihydrotachysterol

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The American Journal of Medicine

Vol. XI SEPTEMBER, 1951 No. 3

Editorial

Clinical Studies

It has been evident for some time, particularly in certain clinical disorders, that some relationship exists between the processes of acidification of the urine on the one hand and the renal regulation of potassium excretion on the other. The precise nature of this relationship has remained obscure. In the present important study of the effects of carbonic anhydrase inhibition, Dr. Berliner and his colleagues demonstrate that suppression of hydrogen ion secretion into the urine leads to increased secretion of potassium by the distal tubules. This suggests competition between hydrogen and potassium ions for a component of the ion exchange mechanism of the renal tubules which is concerned also with reabsorption of sodium in the distal tubules. Such an interrelationship has clinical as well as physiologic implications.

Potassium-losing nephritis, with low potassium syndrome, is an interesting disorder with implications of both clinical and physiologic interest. The case described was followed for a long time and extensively studied. Among other significant points established were evidence of tubular excretion of potassium on a high potassium intake and indications of a reciprocal relationship between potassium and sodium balances.

The authors present three well studied cases of renal tubular acidosis and summarize the findings in fourteen additional cases in the literature. This new syndrome is not only of exceptional physiologic interest but also of considerable clinical significance and moreover responds very readily to simple treatment.

Contents continued on page 5

Every diabetic survey emphasizes the startling percentage of unknown diabetics in our population—and increasing longevity is constantly adding to this total.

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		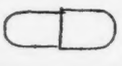		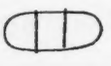
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1. Cullick, L., and Ogden, H. D.: J. So. Med. Assn., 43:643, 1950

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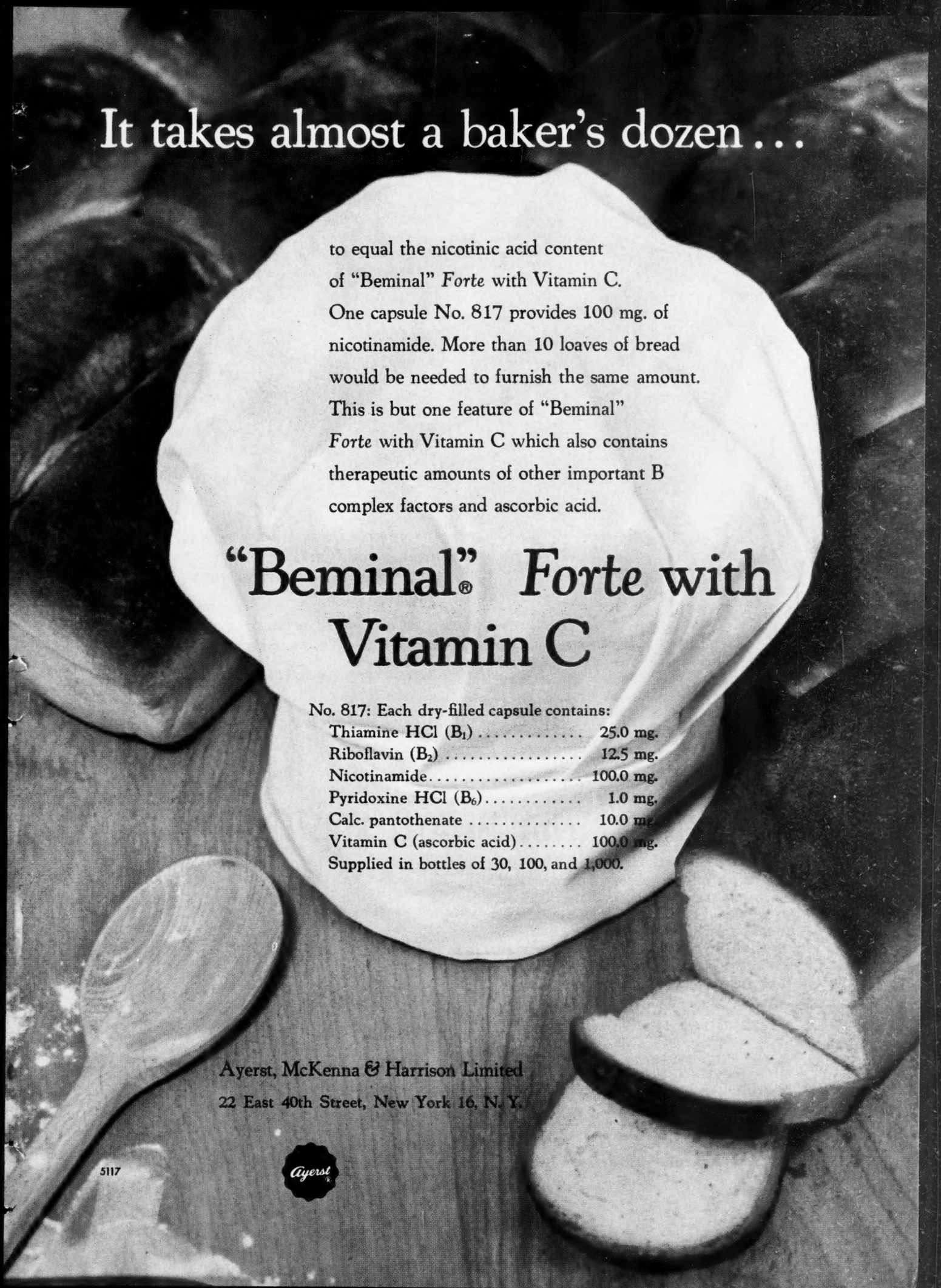
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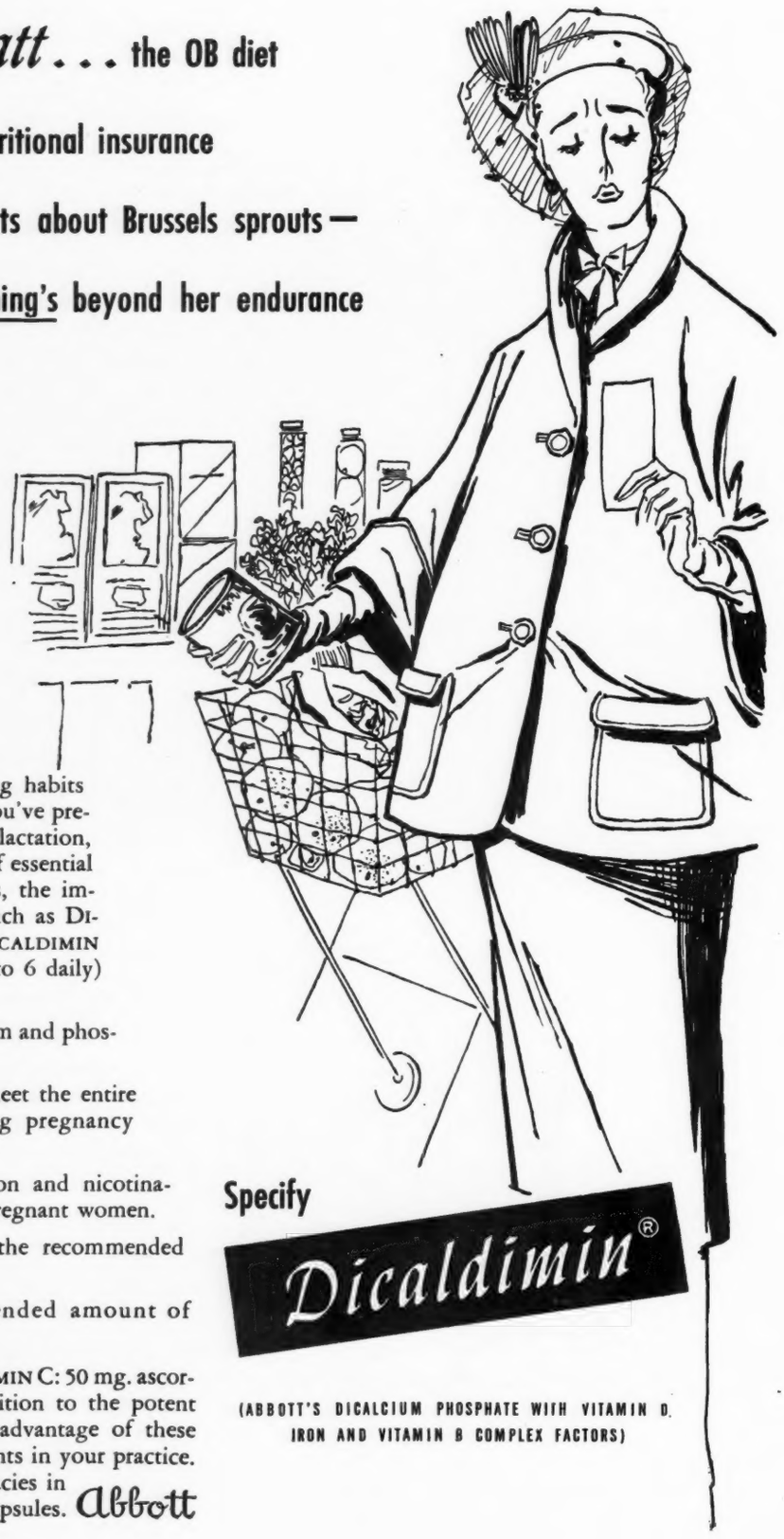

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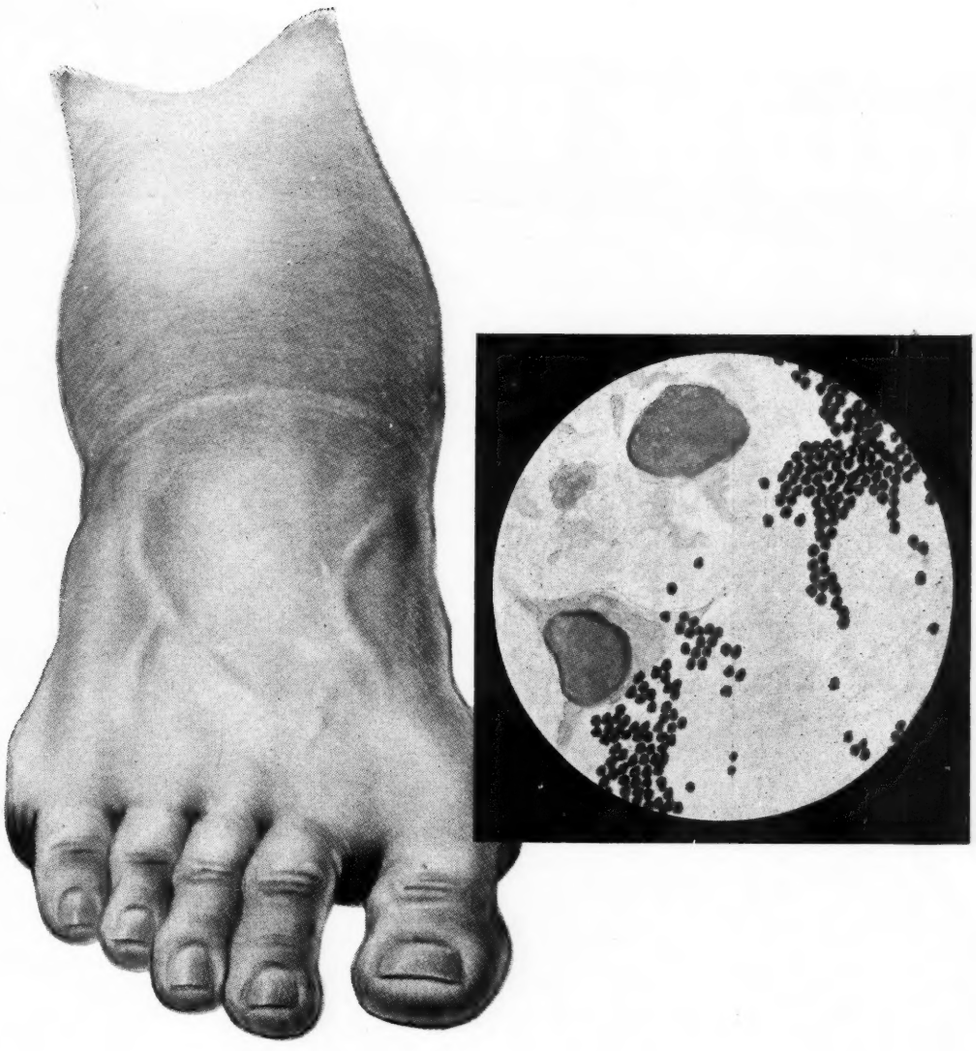

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Killough, J. H.; Magill, G. B., and Smith, R. C.: J.A.M.A. *145*:533 (Feb. 24) 1951.

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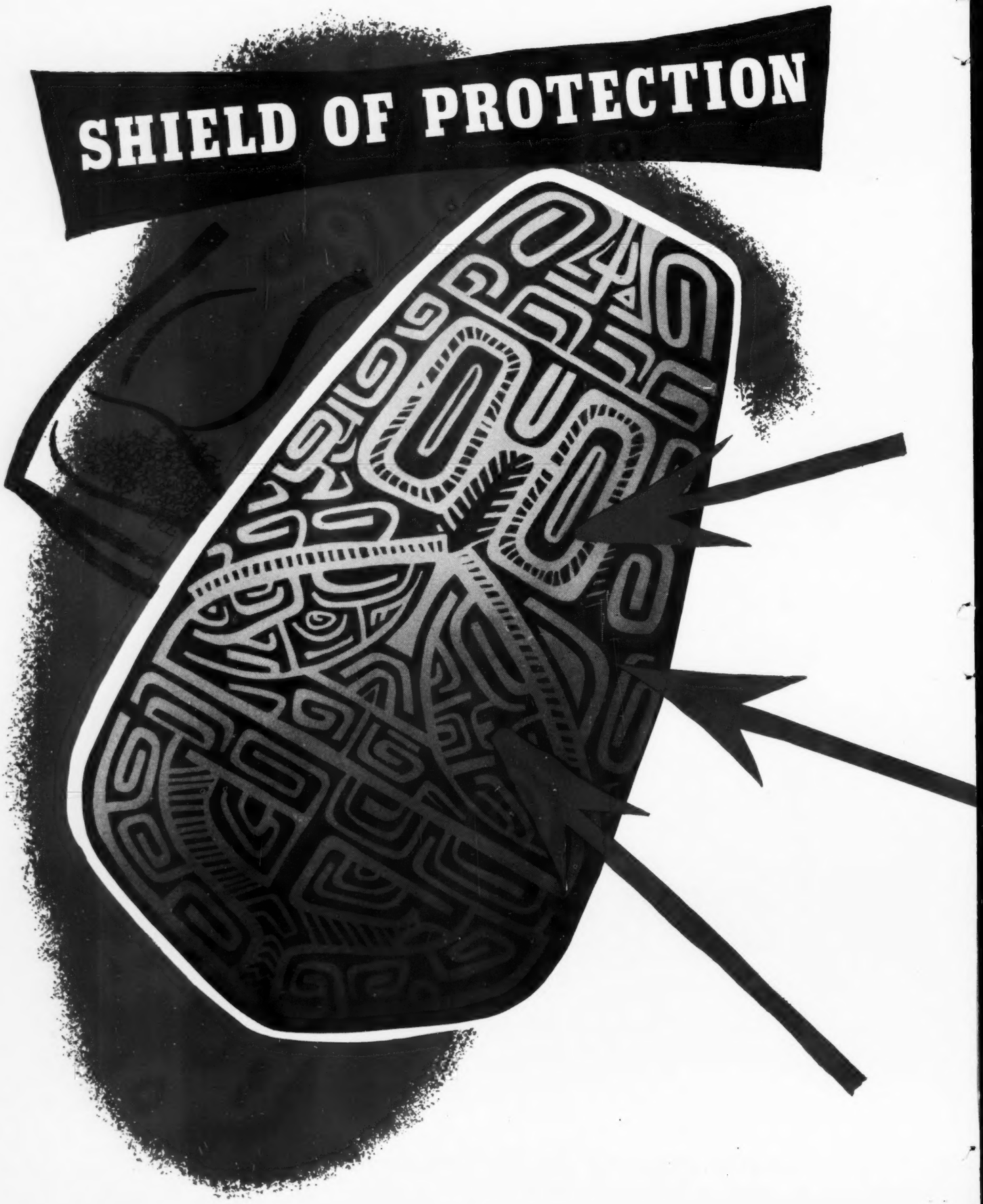

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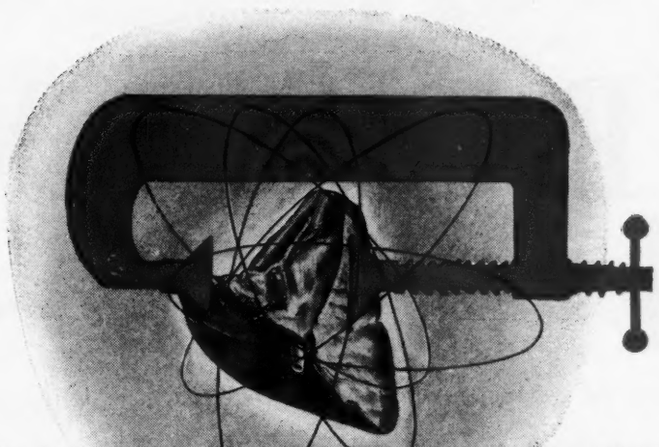

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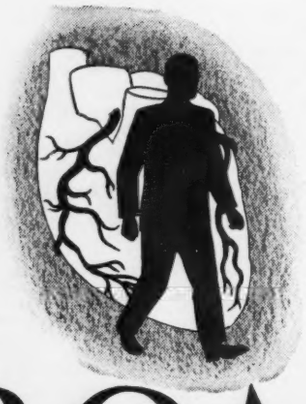

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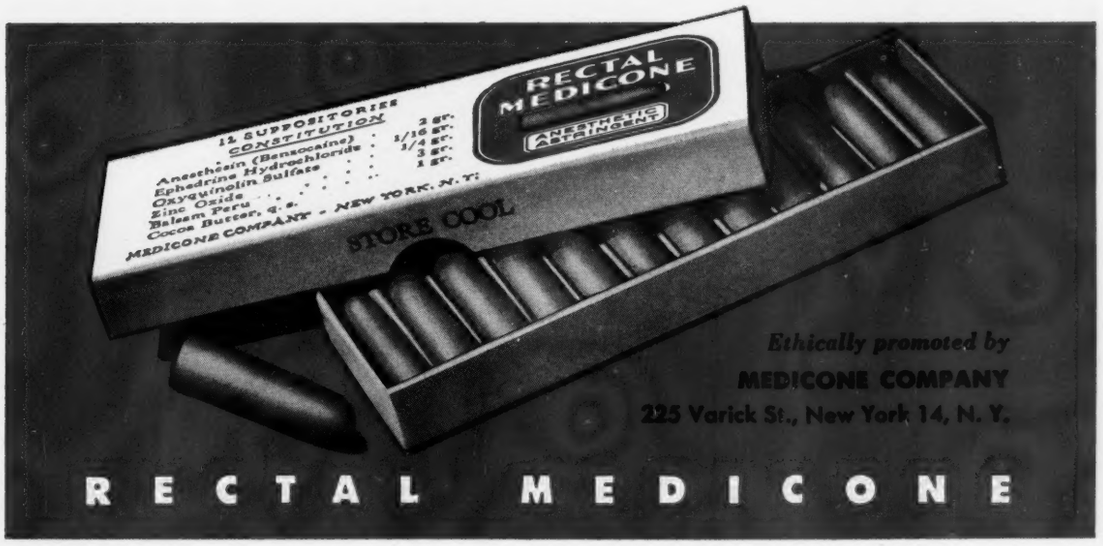

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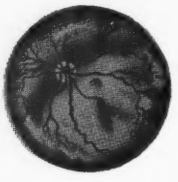

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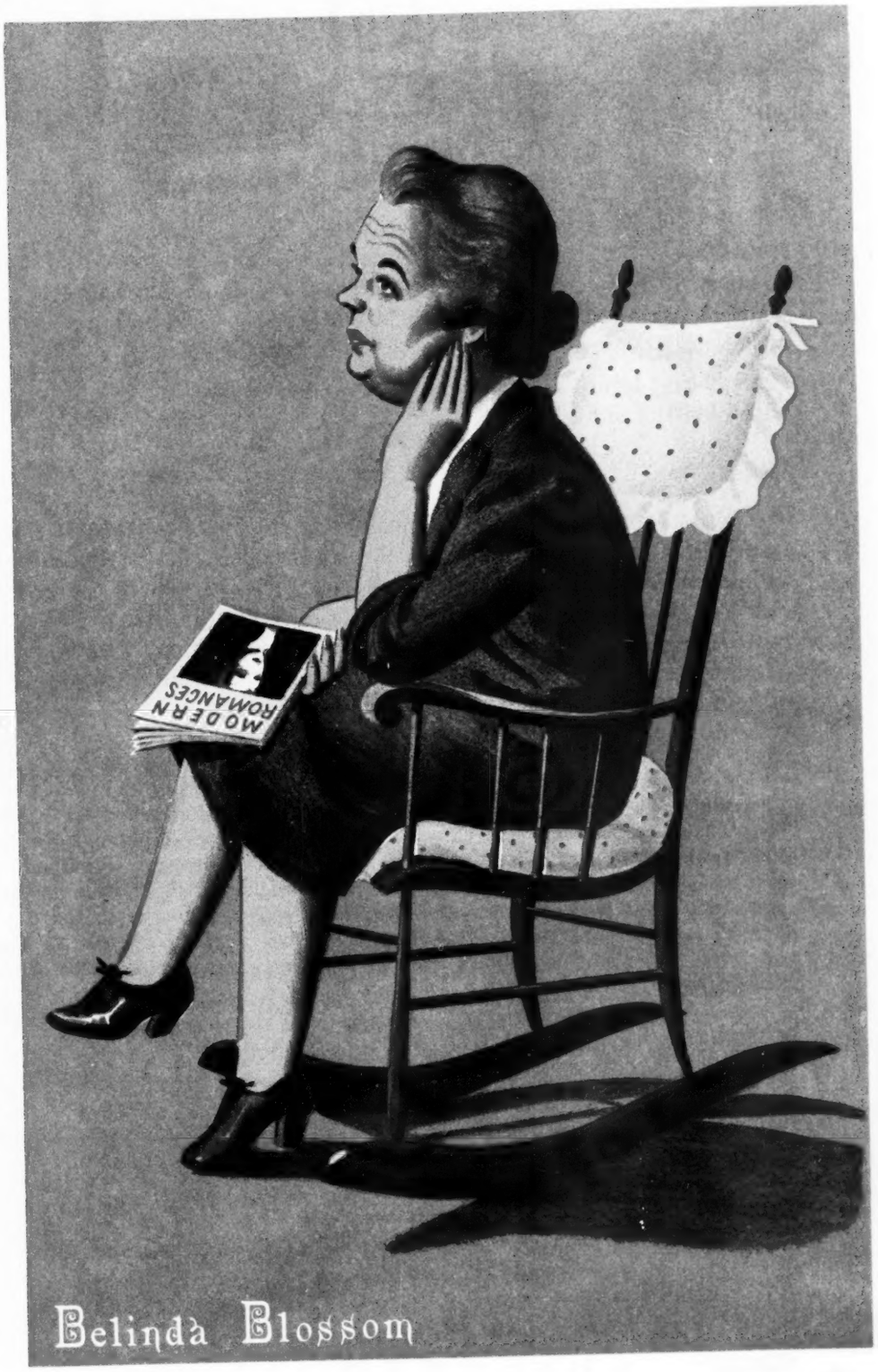

bored, buxom, and bilious . . .

BELINDA BLOSSOM has lost her bloom and given up trying to find it — bemused in her penchant for nostalgic dreams, while stuffing her stomach with caramel creams, she's content just to bide on her broadening beams while the rest of the world goes by . . .

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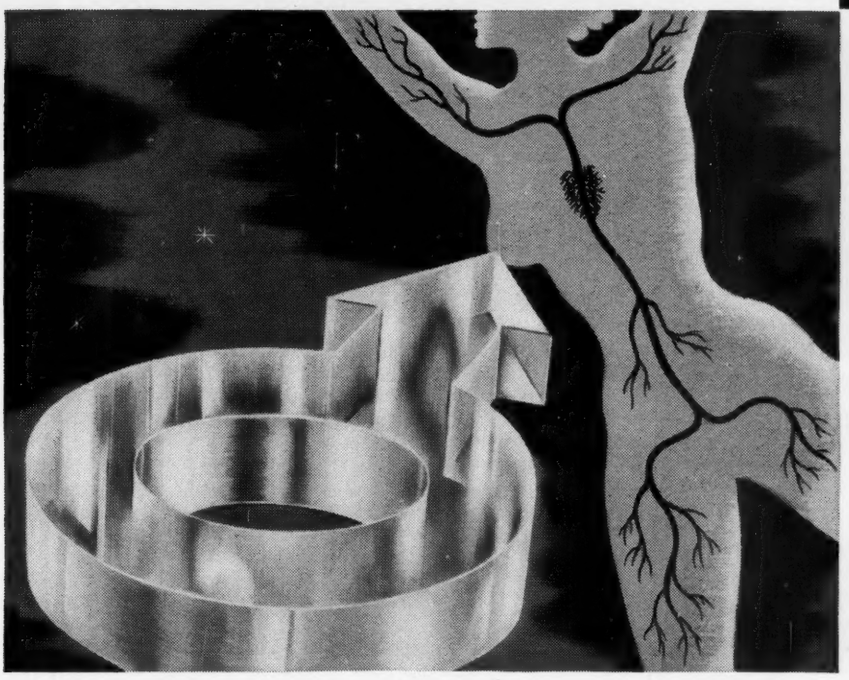

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1. Orr, H. S.: J. Oklahoma M. A. 43:451 (Oct.) 1950.
2 Rabinowitch, I. M.: Am. J. Digest. Dis. 16:322 (Sept.) 1949.

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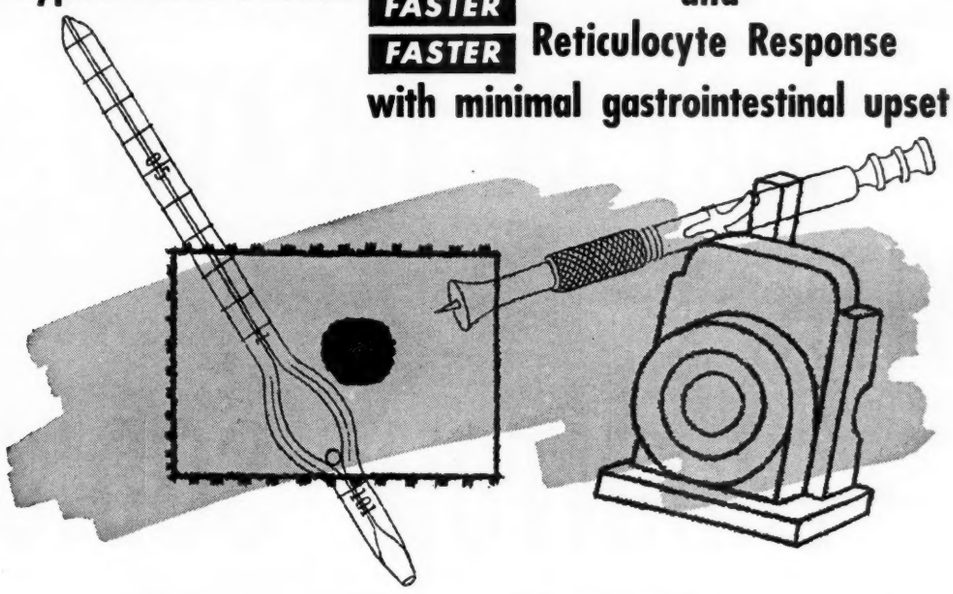

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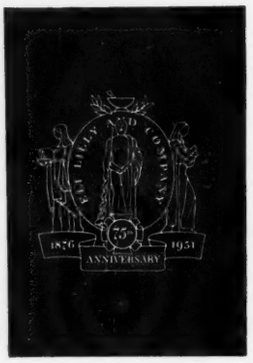

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Editorial

Blood Lipids and Atherosclerosis*

ATHEROMATOSIS of the coronary, cerebral, renal, leg and other vessels is the leading cause of disability and death in this country. As more of the population survives to the later decades the problem of atheromatosis is destined to assume ever increasing importance. It is hardly surprising, therefore, that a voluminous literature is being steadily enlarged by clinical, pathologic, biochemical, experimental and physicochemical investigations.[1] Out of this multidirectional research involving different technics and various experimental subjects the dim outline of the nature of the disorder is beginning to emerge.

Following the demonstration of lipids in atheromatous lesions the starting point of many investigations has been the experimental production of the lesion in the rabbit by feeding large amounts of cholesterol. The deposition of cholesterol and other lipids in the lesions has emphasized the possible etiologic significance of these substances. Likewise the serum cholesterol levels of patients with arteriosclerotic coronary artery disease has been found, in general, to be somewhat higher and to fluctuate more widely than in others not so afflicted.

The significance of these findings is not entirely clear in the light of other data, however. Thus many individuals with widespread involvement of the coronary and other arteries have normal cholesterol and phospholipid values; conversely, elevated values may be present in those not so afflicted. Moreover, cholesterol feeding in animals other than the rabbit may not result in the characteristic lesions. In the dog, Steiner and Kendall[2] found that while large amounts of thiouracil and cholesterol fed to dogs produced atherosclerosis, either agent alone failed to do so. Moreover, simultaneous administration is not effective in the rat.[3] The large amounts of cholesterol and of thiouracil required are unphysiologic and indicate the advisability of caution in transposing the results in experimental animals directly to the problem of atherosclerosis in man. In the chick, atherosclerosis has been induced by diets containing more moderate amounts of cholesterol. But the spontaneous arteriosclerotic lesions of the chick occur despite cholesterol-free, fat-poor diets.[4] Many clinical studies indicate, however, a low correlation between the increased blood lipids and coronary arteriosclerosis although there are individual exceptions. It appears that the concentration of serum cholesterol is probably not the sole determining factor in the production of

[1] GUBNER, R. and UNGERLEIDER, H. E. Arteriosclerosis. A statement of the problem. *Am. J. Med.*, 6: 60, 1949.

[2] STEINER, A. and KENDALL, F. C. Atherosclerosis and arteriosclerosis in dogs following ingestion of cholesterol and thiouracil. *Arch. Path.*, 42: 433, 1946.

[3] HORLICK, L. and HAVEL, L. The effect of feeding propylthiouracil and cholesterol on the blood cholesterol and arterial intima in the rat. *J. Lab. & Clin. Med.*, 33: 1029, 1948.

[4] KATZ, L. N. and STAMLER, J. Experimental Atherosclerosis. Springfield, Ill., 1951. Charles C Thomas.

* From the Department of Medicine of the Harvard Medical School; the Medical Research Department of the Yamins Research Laboratories and the Medical Service, Beth Israel Hospital, Boston, Mass.

atherosclerosis, nor is it certain that moderate differences in the serum cholesterol and phospholipid level in man have any influence on its development. Nevertheless, many attempts have been made to lower the serum cholesterol by dietary and other means.

In a recent communication Keys[5] reports careful studies for over three years on 482 clinically "normal" men who were classified into five groups according to their dietary cholesterol intake. The mean intake of the top group was considered to be about two and one-half times that of the bottom group. The serum cholesterol level of these subjects, whose ages ranged from eighteen to fifty-five years, was not significantly related to differences in the habitual cholesterol intake over a range of approximately 250 to 800 mg. per day. In a separate study of forty-one middle-aged men in whom the cholesterol intakes were reduced 50 per cent or more for at least several months no change in serum cholesterol values was observed. On a substantially fat-free and cholesterol-free rice-fruit diet, which provided little sodium and was likely to be calorically deficient as well, four hypertensive patients showed a fall in the mean total cholesterol value from 233 mg./100 ml. of serum to an average of 152 mg. after about three weeks. Keys points out that it is doubtful whether most so-called low cholesterol diets in current use have significant utility for their purpose. This is not altogether surprising since cholesterol can be synthesized in the body from acetate which is available from the metabolism of fat, glucose and protein. Diets that permit ordinary amounts of lean meats and the use of skim milk, and that do not rigidly exclude from every item of cooking and baking all dairy products, eggs and animal products, will regularly supply more than 100 mg. or even as much as 200 mg. of cholesterol daily; a much more rigorous diet is required to lower the cholesterol levels. Even on a quite free cholesterol regimen the addition of vegetable oils may promote cholesterol rises in the blood serum. Some success has been claimed in lowering the serum cholesterol by lipotropic agents such as choline, inositol and lecithin but their clinical usefulness is doubtful.

Recent studies suggest that the size and physical state of the lipid molecules may be of greater etiologic significance than the serum concentration of cholesterol and perhaps of other lipids. Hueper[6] observed that repeated injections of polyvinyl alcohol, pectin and other macromolecular substances in dogs, rabbits and rats resulted in lesions which in their morphologic appearance and distribution were characteristic of atherosclerosis except that the deposits were of an injected foreign substance instead of lipids. He referred to the lesions as macromolecular atherosclerosis. Moreton[7] observed, after the ingestion of a fatty meal, markedly greater numbers of lipid particles of considerably larger size than those found in normal fasting plasma or after fat-free meals. He proposed the theory that the cumulative effect of many fatty meals over a lifetime, by producing these transient showers of large lipid particles in the plasma, might be the underlying cause of the intimal lipid deposition in human atherosclerosis. He suggested that lipid deposition primarily in the tissue spaces of the arterial intima could be ascribed to the increased particle size which leads them to be retained or deposited by the barrier of the fenestrated internal elastic membrane of the intima.

A new approach to the study of the problem was introduced by Gofman, Jones and their associates[8] by ultracentrifugal flotation of the serum cholesterol and other serum lipids in the analytic ultracentrifuge.

[5] Keys, A., Mickelsen, O., Miller, E. V. O. and Chapman, C. B. The relation in man between cholesterol levels in the diet and in the blood. *Science*, 112: 79, 1950.

[6] Hueper, W. C. Organic lesions produced by polyvinyl alcohol in rats and rabbits. A toxicopathologic investigation of an experimental thesaurosis. *Arch. Path.*, 28: 510, 1939.

[7] Moreton, J. R. Atherosclerosis and alimentary hyperlipemia. *Science*, 106: 190, 1947.

[8] Gofman, J. W., Jones, H. B., Lindgren, F. T., Lyon, T. P., Elliott, H. A. and Strisower, B. Blood lipids and human atherosclerosis. *Circulation*, 2: 161, 1950.

They have studied the presence of the various macromolecular complexes in normal persons of various ages and in patients with coronary artery disease, diabetes mellitus and other states which are commonly believed to predispose to premature and marked atherosclerosis. They have been able to identify and quantitate groups of molecules of various densities as they undergo flotation by this method. Of the four classes of molecules found in the serum, one class in particular includes at least three species which migrate with rates between 10 and 20 units expressed in terms of flotation rates, S_f. This class, according to Gofman, appears to be related to atherosclerosis in humans. Each of the three species contains approximately 30 per cent cholesterol by weight. The class of molecules with rates between 3–8 S_f units evidently carries a major fraction of the serum cholesterol and does not appear related to atherosclerosis. In 230 males with myocardial infarction 91 per cent showed the presence of S_f 10–20 molecules above the borderline resolution value, compared with approximately 50 per cent of control subjects. This suggests that the presence of these molecules in the serum is in some way associated with the presence of atherosclerosis. The finding of these molecules in over 40 per cent of 226 normal males between twenty and thirty years of age raises the question of whether these are the persons destined to atherosclerosis. Only observations over many years can clarify this problem. Although there is a general trend toward higher S_f 10–20 concentrations with higher serum cholesterol levels, in any particular patient the analytic serum cholesterol level is of no value in predicting the concentration of S_f 10–20 molecules. A group of men and women placed on a low fat, low cholesterol diet showed consistent trends to lower concentrations of the S_f 10–20 molecules over a period of weeks to months. These investigations raise many significant questions such as which of the molecules found in the blood are deposited in the atheromatous lesions, the significance of the other classes of molecules, the chemical nature of the molecules and their metabolic role.

Other investigations[9] indicate that the deposition of lipid compounds may not be determined by absolute levels of total lipid concentration nor by the absolute level of any single lipid fraction. The ratio of cholesterol to phospholipid may be of particular significance, relatively high concentrations of the phospholipids acting to "solubilize" the hydrophobic cholesterols and neutral fats.

Atherosclerosis produces its dire effects by its localization in the brain, coronary arteries, renal, leg and other vessels. In some instances a single strategic lesion in the coronary arteries produces death whereas extensive atheromatous lesions of the aorta may be compatible with longevity. Intravascular pressure and injury seemingly play an important role but our understanding of the factors which determine localization of the lesions is incomplete. Intrinsic vascular damage as well as general metabolic influences must be considered. The important insight gained to date regarding many phases of atherosclerosis, however, presages rapid strides in our understanding of the disorder.

HERRMAN L. BLUMGART, M.D.

[9] AHRENS, JR., E. H. The lipid disturbance in biliary obstruction and its relationship to the genesis of arteriosclerosis. *Bull. New York Acad. Med.*, 26: 151, 1950.

Clinical Studies

Relationship between Acidification of the Urine and Potassium Metabolism*

Effect of Carbonic Anhydrase Inhibition on Potassium Excretion

ROBERT W. BERLINER, M.D., THOMAS J. KENNEDY, JR., M.D. *and* JACK ORLOFF, M.D.
Bethesda, Maryland

A RELATIONSHIP between potassium metabolism and the reaction of the body fluids has long been recognized and has been defined largely through the work of Darrow and his associates.[1,2] It has been noted that potassium depletion in Cushing's syndrome is accompanied by alkalosis,[3,4] that similar alkalosis and potassium depletion may be produced by some of the adrenal cortical steroids in man and experimental animals[1,5] or by dietary potassium deficiency in the rat.[1,6] Conversely, an increase in muscle potassium concentration has been found to accompany acidosis.[1,6] In the absence of marked extrarenal losses of fluid and electrolyte and without unusual intake of fixed cation or anion, it is clear that these related changes in body potassium and the reaction of body fluids must be brought about by some modification of renal activity, an excess of acid being excreted when body potassium is depleted and relative retention of potassium occurring in the presence of acidosis. Evidence that such changes in renal excretion actually occur can be adduced from the observations that administration of potassium salts leads to the production of an alkaline urine and acidosis of the body fluids[7–9] while depletion of potassium has been found to be associated with the production of an acid urine in the face of marked increases in plasma pH and bicarbonate.[10,11] The basis for the interdependence of potassium excretion and urine acidification has not been clearly understood. The experiments to be reported here appear to clarify the nature of this relationship and indicate that there is competition between hydrogen and potassium ions at some common point in their secretory pathway.

It has been demonstrated that secretion of potassium ions by the renal tubules is required to account for the potassium excretion which may be induced by rapid rates of potassium administration or by hypertonic solutions[12,13] and that this secretory process is one of ion exchange, potassium ions within the cells of the distal tubule being exchanged for sodium ions from the tubular lumen.[9] In this respect the mechanism for potassium excretion parallels that previously elucidated by Pitts and his associates for acidification of the urine,[14,15] since it had been shown that secretion of hydrogen ions is required to account quantitatively for the process by which the urine is acidified and bicarbonate reabsorbed in the distal tubule. Furthermore, presumptive evidence had been presented that this secretory process is fundamentally one of ion exchange, hydrogen ions derived from the metabolic activity of cells being exchanged for sodium ions from the lumen of the tubule. It was also shown that carbonic anhydrase was a component of the system by which hydrogen ions were made available for this ion exchange process since the administration of sulfanilamide, an inhibitor of carbonic anhydrase, was found to reduce the excretion of acid.[14,15]

Since the process by which the urine is acidified† is also one by which sodium is reabsorbed,

† It has been pointed out[15,16] that the secretion of ammonia is best explained as the diffusion of ammonia into the acidified contents of the lumen of the distal tubule where combination with hydrogen ions yields

* From the Section on Kidney and Electrolyte Metabolism, National Heart Institute, National Institutes of Health, United States Public Health Service, Federal Security Agency, Bethesda, Md.

it was suggested that a drug which would inhibit this mechanism might be a useful diuretic in cardiac decompensation.[17] Sulfanilamide was found to be partially effective in causing sodium loss in cardiac failure but, because of its rather low order of activity as an inhibitor of carbonic anhydrase and its many undesirable side effects, its use was discontinued.[17] However, a search for more active carbonic anhydrase inhibitors was instituted and the synthesis and *in vitro* activity of a number of such compounds has been reported.[18,19] The experiments to be reported here make use of one of these compounds, 2-acetylamino 1,3,4-thiadiazole-5-sulfonamide (No. 6063),* which has the structural formula indicated in Figure 1 and an activity *in vitro* 330 times that of sulfanilamide for the 50 per cent inhibition of carbonic anhydrase activity.

MATERIALS AND METHODS

Experiments were performed using trained, unanesthetized female dogs weighing 16 to 25 kg. All solutions were administered by continuous intravenous infusion using a calibrated pump. Urine was collected from indwelling catheters. Each clearance period was terminated by washing the bladder twice with distilled water and *without* the introduction of air. Urine for the determination of pH and CO_2 content was collected anaerobically directly into syringes coated with silicone stop-cock grease and with the dead space filled with a small amount of mineral oil. To obtain these specimens with minimal loss of free CO_2 the bladder was emptied by manual pressure at approximately the mid-point of each period, the syringe attached to the catheter and a 5 or 10 cc. sample obtained as rapidly as it collected in the bladder. The collection of urine during the remainder of the clearance period was made in the conventional manner.

Blood samples were collected at the mid-point of each clearance period from an indwelling femoral arterial needle. Specimens were received into oiled syringes to which a few drops of a solution of heparin had been added. Samples for the determination of pH and CO_2 content

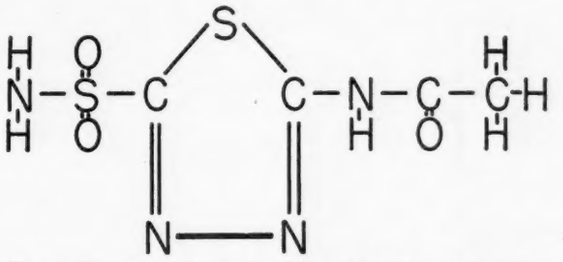

FIG. 1. Structural formula of No. 6063 (2-acetylamino-1,3,4-thiadiazole-5-sulfonamide).

were placed in centrifuge tubes under a layer of mineral oil and analyses were made as soon as the plasma had been separated.

Creatinine was determined in trichloroacetic acid filtrates of plasma and in diluted urine (to which equivalent amounts of trichloroacetic acid were added) by a modification of the Folin method.[20] Inulin in zinc filtrates of plasma and urine was determined by the method of Harrison.[21] Fermentable substances were removed from both plasma and urine by treatment with yeast before precipitation. Sodium and potassium in diluted plasma and urine were determined by internal standard flame photometry.[22,23] Chloride in plasma and urine was determined by a modified Volhard titration, phosphate in trichloroacetic acid filtrates of plasma and diluted urine by the method of Fiske and SubbaRow,[24] CO_2 content of plasma and urine by the method of Van Slyke and Neill.[25] The pH of whole blood and of urine was measured in a Beckman model G pH-meter using a syringe-type glass electrode. The pH of blood was measured at room temperature and corrected to body temperature by subtracting 0.014 pH units per degree c. The pH of urine was measured at 37°c. Concentrations of bicarbonate and free CO_2 were calculated from the Henderson-Hasselbach equation using a pK of 6.1 for carbonic acid.

The clearance of inulin, creatinine or both was used as a measure of the rate of glomerular filtration. The amount of potassium filtered was calculated as the product of filtration rate and plasma potassium concentration corrected by a factor of 0.95 for the Donnan equilibrium.

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ammonium ions. Hence, it may be considered that the secretion of a hydrogen ion is the primary event in the excretion of an ammonium ion. Quantitatively, changes in ammonia excretion may often be more important than changes in titratable acidity. Throughout this paper it is intended that the term "acidification of the urine" be understood to include the hydrogen ion secreted, whether appearing as ammonia or titratable acidity or dissipated in the conversion of bicarbonate to CO_2 and water.

* Supplied through the courtesy of Dr. R. O. Roblin, Jr. of American Cyanamid Company.

RESULTS

A single intravenous dose of 10 mg./kg. of No. 6063 was found to abolish any evidence of urine acidification in the presence of fairly severe acidosis. The effect tended to diminish fairly rapidly with time but could be sustained

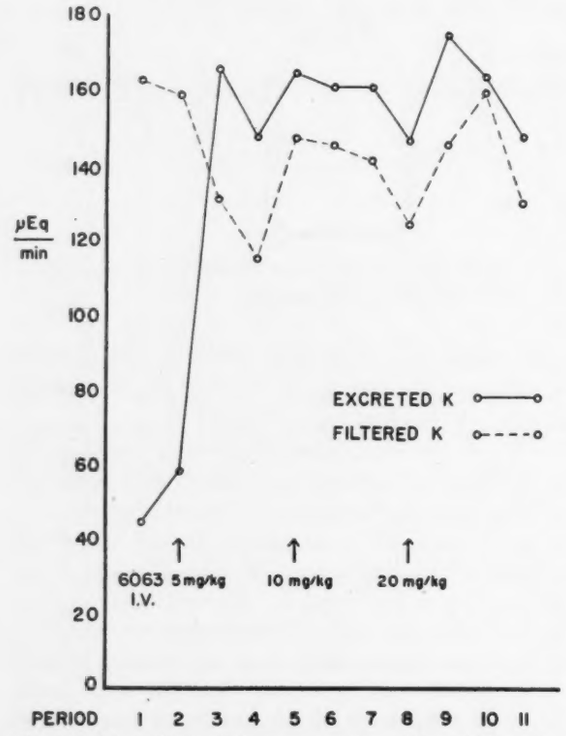

FIG. 2. Effect of No. 6063 on excretion of potassium. No appreciable increase in potassium excretion results from increased dosage beyond 5 mg./kg.

by infusion of the drug at a rate of 20 mg./kg./hour. No appreciable difference in the effect on either urine acidification or potassium excretion could be detected with doses varying from 5 to 20 mg./kg. so that presumably the dosage used was sufficient to produce a near maximal inhibition of renal carbonic anhydrase activity. The drug had the predictable action in abolishing titratable acidity and increasing bicarbonate excretion. The experiments to be reported are concerned with the effects on potassium excretion, and other data will be referred to only insofar as they are pertinent to the potassium effects. A finding not directly related to the excretion of potassium was a drop in the rate of glomerular filtration which occurred immediately after the administration of No. 6063 in all but a few experiments. The depression of filtration rate generally persisted throughout the period of the action of the drug and usually was of the order of 20 to 40 per cent. Presumably, this was a change in the rate of glomerular filtration and not in the permeability of the tubules since there was no change in the relationship of creatinine clearance to inulin clearance. There was no obvious effect of the drug observed other than those on renal function. The animals remained in excellent health despite repeated experiments and recovered the capacity to excrete an acid urine at least within twenty-four hours.

Administration of No. 6063 was invariably followed by an increase in potassium excretion. The extent of this increase varied with the circumstances. The increase in potassium excretion relative to the amount filtered was most striking in moderatedly acidotic dogs or in dogs in normal acid-base balance when the animals were not receiving potassium by infusion. In a few instances the increment in potassium excretion was equal to or greater than the total potassium contained in the glomerular filtrate. Such changes could be explained only by an increase in secretion of potassium by the renal tubules since even total elimination of reabsorption, previously complete, could not account for an increase of this magnitude in the excretion of potassium. Experiments showing the effect of No. 6063 on potassium excretion are presented in Table I and Figure 2. In dogs rendered alkalotic by the infusion of $NaHCO_3$ the excretion of potassium was high initially and increased only slightly following the injection to No. 6063. When potassium excretion was elevated by the infusion of potassium salts, inhibition of carbonic anhydrase produced a variable increase in the amount of potassium excreted; the ratio of excreted to filtered increased markedly, in part because of a decrease in glomerular filtration rate.

The increment in potassium excretion resulting from carbonic anhydrase inhibition did not exceed the amount filtered in many of the experiments nor, in others, was the margin sufficient to indicate with certainty that the increase was due solely to increased secretion rather than decreased reabsorption. Therefore, additional experimental verification of this thesis was sought. Since the mercurial diuretics are known to have striking effects on potassium excretion,[12,36] the effects of salyrgan and No. 6063, acting individually and simultaneously, were studied. The results of two such experiments are shown in Figure 3 and Table II.

TABLE I

EFFECT OF NO. 6063 ON ELECTROLYTE EXCRETION--DOG D--WEIGHT 18 KG.

Time (min.)	Urine Flow (ml./min.)	Urine pH	Inulin Clearance (ml./min.)	Plasma K^+ (mEq./L.)	Plasma HCO_3^- (mEq./L.)	Excreted Na^+ (μEq./min.)	Excreted K^+ (μEq./min.)	Excreted Cl^- (μEq./min.)	Excreted HCO_3^- (μEq./min.)	Excreted Phosphate (μM/min.)	Filtered K^+ (μEq./min.)	Excreted/Filtered K^+
-80	Priming infusion: Inulin 1.0 gm. in 30 cc. H_2O i.v.											
-61	Start sustaining infusion: Inulin 9 mg./min.; Na_2HPO_4.NaH_2PO_4 (pH 7.4) 175 μM/min. in H_2O at 1.08 ml./min.											
0-22	1.17	7.18	78	3.0	23	93	89	37	33	58	222	0.40
22-43	0.62	7.03	73	3.0	23	71	74	14	16	62	208	0.36
43-64	0.75	7.06	74	3.0	23	98	76	12	25	78	211	0.36
71-73	No. 6063 10 mg./kg. i.v.; 20 mg./kg./hr. of No. 6063 added to infusion											
79-94	3.40	7.76	56	2.7	23	403	245	35	392	95	144	1.70
94-106	2.98	7.72	53	2.6	23	368	188	29	328	94	131	1.43
106-121	2.75	7.69	54	2.8	23	363	201	20	300	114	143	1.41
121-135	3.08	7.68	54	2.6	23	374	202	18	284	135	133	1.52
135-148	3.02	7.60	55	2.5	23	389	198	16	272	151	130	1.52

TABLE II

EFFECT OF SALYRGAN, NO 6063, AND BAL ON ELECTROLYTE EXCRETION--DOG V--WEIGHT 17 KG.

Time (min.)	Urine Flow (ml./min.)	Urine pH	Creatinine Clearance (ml./min.)	Plasma K^+ (mEq./L.)	Plasma Na^+ (mEq./L.)	Plasma HCO_3^- (mEq./L.)	Excreted Na^+ (μEq./min.)	Excreted K^+ (μEq./min.)	Excreted Cl^- (μEq./min.)	Excreted HCO_3^- (μEq./min.)	Excreted Phosphate (μM/min.)
-69	Sustaining infusion: Creatinine 11.0 mg./min.; Na_2HPO_4.NaH_2PO_4 (pH 7.4) 169 μM/min.; NaCl 395 μM/min.; H_2O 4.5 ml./min.										
-62	Priming infusion: Creatinine 2.0 gm.										
0-19	1.89	6.80	72	3.5	147	20	282	74	149	21	126
19-38	2.06	6.82	76	3.2	145	20	310	62	137	24	152
41	2 ml. salyrgan-theophylline i.v; 1 ml. salyrgan-theophylline added to infusion										
64-74	8.54	6.96	76	3.2	146	18	1280	59	1010	79	162
74-84	10.15	6.77	68	3.3	147	18	1390	60	1190	57	167
84-94	10.50	6.63	67	3.0	145	18	1440	61	1280	42	165
97	10 mg./kg. No. 6063 i.v.; 30 mg./kg./hr. of No. 6063 added to infusion										
108-118	11.06	7.38	50	3.1	145	18	1790	68	1150	350	150
118-128	10.41	7.39	57	3.1	146	19	1750	68	1150	384	165
128-138	9.30	7.41	56	---	148	19	1670	69	1100	392	144
139	90 mg. BAL i.m.										
154-169	2.75	7.82	58	3.0	146	18	499	171	72	354	123
169-186	3.21	7.81	60	2.8	---	--	552	128	120	362	111
186-203	3.90	7.65	70	2.6	148	17	641	139	147	371	144

Following two control periods a dose of salyrgan-theophylline was administered; the characteristic increase in the excretion of sodium and chloride was produced. The minimal changes in potassium excretion are in accord with previous observations. After three periods showing the effect of mercurial alone, No. 6063 was administered at a dosage of 10 mg./kg. intravenously initially followed by an infusion at the rate of 20 mg./kg./hour for the remainder of the experiment. The inhibition of hydrogen ion secretion is indicated by the striking increase in bicarbonate and sodium excretion, the increment of the latter being added to that attributable to the mercurial. The increase in potassium excretion was however minimal, in contrast to the effect usually observed following administration of No. 6063. After three periods to observe the combined effects of mercurial and carbonic anhydrase inhibitor the effect of the mercurial diuretic was abolished by the intramuscular administration of 5 mg./kg. of BAL.[27] The last three periods show the usual effects of No. 6063 alone. The excretion of potassium rises to a high level, bicarbonate excretion continues at a rapid rate, chloride excretion returns to a low level, and sodium excretion diminishes more or less in parallel with the decreased loss of chloride.

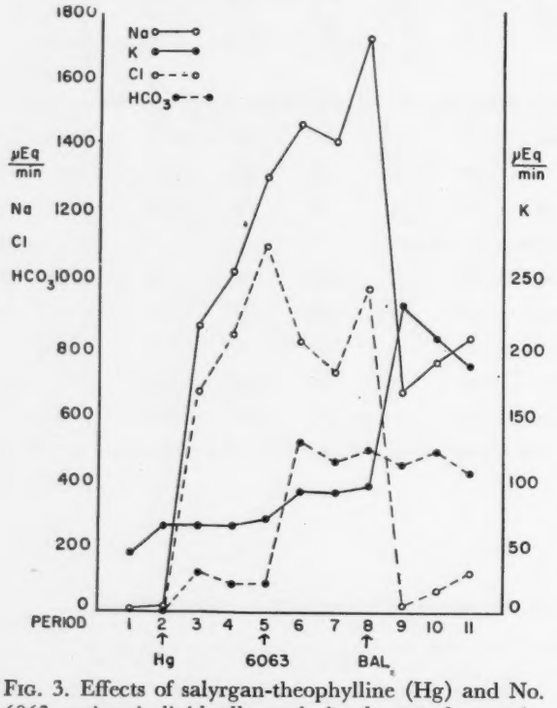

FIG. 3. Effects of salyrgan-theophylline (Hg) and No. 6063 acting individually and simultaneously on the excretion of electrolytes during the infusion of sodium phosphate (pH 7.4) solution. Periods 1 and 2, control; periods 3–5, effect of mercurial alone; periods 6–8, effect of both mercurial and No. 6063; periods 9–11, effect of No. 6063 alone after removal of mercurial action by BAL. Note that scale for potassium excretion is four times that for other electrolytes.

Differing explanations for the effect of mercurial diuretics on potassium excretion have been offered. It has been implied[12] that the effect is produced by an increase in the reabsorption of potassium in the proximal tubule such as might be caused by diversion of a mechanism for the reabsorption of sodium to the transport of potassium instead. On the other hand, Mudge et al.[26] have proposed that the effect is attributable to inhibition of both reabsorption and secretion of potassium in the proximal and distal tubules, respectively. Combinations of the various possible effects of mercurial and No. 6063 are presented diagrammatically in Figure 4. The assumption is made that if one drug inhibits a transport mechanism, any enhancing effect of the other on this mechanism will be ineffective. A consideration of this figure will indicate that all combinations of the two drugs acting together would yield a high rate of potassium excretion except that represented by the combination of increased secretion due to No. 6063 and inhibition of secretion due to mercurial. It is therefore concluded that the increase in potassium excretion which follows inhibition of carbonic anhydrase is due to increased secretion of potassium by the distal tubules.

COMMENTS

The fact that elimination of hydrogen ion secretion into the urine leads to increased secretion of potassium by the renal tubules* is in accord with the concept that there is competition between hydrogen and potassium ions for some component of the ion exchange mechanism whereby sodium is reabsorbed in the distal tubules. This is likewise in accord with the observed relationships between body potassium and potassium excretion on the one hand and the reaction of body fluids and acidification of the urine on the other. Despite the general tendency to acidosis produced by inhibition of renal carbonic anhydrase, the effect on renal tubule cells may be considered one of relative alkalosis since available hydrogen ion is reduced.

* A review of the data obtained during the inhibition of urinary acidification with maleate[28] indicates that a similar rise in potassium excretion occurred.

The effect on the cells involved in the ion exchange mechanism might be expected to be similar to that associated with alkalosis of the body fluids under other circumstances. Exchange of potassium for sodium rather than of hydrogen for sodium would be favored and potassium loss suppressed and an alkaline urine would be produced. The loss of base that excretion of an alkaline urine implies would lead to the production of acidosis. On the other hand, when the body is depleted of potassium, the normal balance between potassium and hydrogen ions is

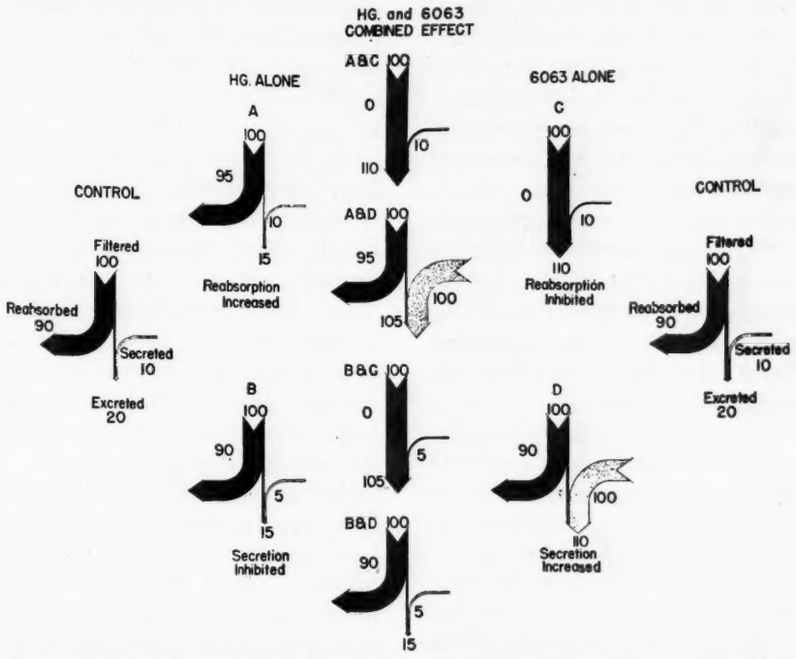

FIG. 4. Schematic representation of processes involved in potassium excretion. Under control conditions, for purposes of presentation, it is assumed that 100 units of potassium are filtered and 90 reabsorbed; to the 10 units remaining 10 are added by secretion to yield an excretion of 20. A slight decrease in excretion due to mercurial may be attributed to either increased reabsorption (A) or decreased secretion (B). The marked increase in excretion due to No. 6063 may be due to inhibited reabsorption (C) or enhanced secretion (D). The four combinations of these two pairs of alternatives are indicated in the middle column. A high rate of potassium excretion would result from all combinations except B and D which alone corresponds to the observed effect. The numerical values, while arbitrarily chosen, are of the magnitude observed in many experiments. Any other values which are consonant with available data[9,12,26] will not modify the conclusions drawn from this figure.

would ensue. On the other hand, in the presence of acidosis one would expect that a greater share of the exchange would be given over to hydrogen ion secretion at the expense of potassium secretion and retention of potassium might be expected. When the changes in potassium are primary, exactly the converse effects would be anticipated. It has been shown in balance experiments that the administration of potassium salts increases the potassium content of cells[29,30] and it may be presumed that the renal tubule cells participate in this process. When potassium concentration in the renal tubule cells is elevated, the exchange of potassium for sodium would be favored, that of hydrogen for sodium tipped in favor of the latter and an acid urine is produced despite the alkalosis which results. Recognizing a competition between potassium and hydrogen ions, these contingencies may reasonably be predicted and are in accord with experimental and clinical observations.

The implications, both physiologic and clinical, of this ionic competition are of considerable importance. It is reasonable that if alkalosis or acidosis can cause, respectively, loss or retention of potassium, normal potassium excretion is at least in part accomplished by the mechanism in which the hydrogen ion plays a competitive role. It is, therefore, probable that potassium secretion by ion exchange is a more or less

continuous process and may well account for much if not all of the normal excretion of potassium. This is in accord with the position stated by Mudge et al.[26] The fact that the urine becomes alkaline, when potassium salts are infused, long before the amount of potassium excreted exceeds the amount filtered[9] is presumably due to increased intracellular potassium concentration and suggests that the increasing potassium excretion is due to secretion. In the latter experiments it was noted that there was an increase in chloride excretion associated with the decreased acidity of the urine when potassium was administered. Similar transient and generally small increases in chloride excretion followed the administration of No. 6063 in the present series of experiments. The explanation of this increase is not entirely clear but it may represent a non-specific effect of the change in pH of the urine on the transport of this anion.

It is worthy of note that the competition between hydrogen and potassium ions for secretion is not on a one-to-one basis, at least insofar as can be detected. The decrement in hydrogen ion excreted which results from inhibition of carbonic anhydrase is considerably greater than the increment in potassium excretion which ensues. This may indicate either that the turnover rate for hydrogen ions is greater than that for potassium or that the reactions which limit the rates of secretion of the two ions are not those involved in the competition. The inequality in turnover affords a possible explanation for the diuretic action of potassium salts, that is, their capacity to cause a loss of sodium. Following the administration of potassium salts the ion exchange mechanism in the distal tubule is diverted in part to potassium exchange. This, in itself, involves no increase in sodium excretion since potassium is exchanged for sodium instead of hydrogen for sodium. However, the suppression of hydrogen ion secretion which accompanies this shift is greater than the increase in potassium excretion. The difference between the increment in potassium secretion and the decrement in hydrogen exchange would represent net loss of sodium.

The present experiments lend support to the thesis that the concentration of potassium in the cells of the renal tubules plays a role of central importance in regulating the rate of potassium excretion.[9,30] This position requires modification, however, to the extent that it is the relationship of potassium to hydrogen ion which is more directly concerned. Other influences, such as anion excretion[9] and endocrine factors, are not of course to be discounted.

Although the experiments which form the basis for the present report were performed in dogs, there is little reason to question their direct application to analogous situations in man. The data concerning the mechanism for acidifying the urine obtained in dogs[14] have been almost duplicated in similar studies in man.[31,32] Although the mechanism for potassium secretion in man has not been studied as extensively as in the dog, sufficient data have been obtained to indicate the existence of analogous capacities.[9] Furthermore, most of the inter-relations between potassium metabolism and urinary acidification which have been found to exist experimentally in animals have been demonstrated either by experiment or in clinical abnormalities in man. Indeed, a rather striking loss of potassium was found to accompany the treatment of cardiac patients with sulfanilamide.[17]

The relationship between potassium metabolism and acid-base balance under consideration here is pertinent to a number of clinical situations. One of the more interesting although more uncommon of these is that syndrome which has been called "tubular insufficiency without glomerular insufficiency"[33] or renal acidosis.[34] This syndrome is characterized by a relative incapacity to acidify the urine, along with a tendency to a negative balance of phosphate, potassium and calcium.[33] In many respects the abnormalities of renal function described in these patients correspond very closely to those in animals in which acidification has been impaired by inhibition of carbonic anhydrase or by the administration of maleate,[28]* The resemblance is so striking as to favor the view that the abnormality in patients with this type of renal acidosis is a specific biochemical defect in the mechanism for secreting hydrogen ions rather than some non-specific damage to the distal tubule. In this situation, as has been pointed out,[34] a low intracellular potassium concentration is associated with acidosis rather than with the usual alkalosis. Presumably, the alkalosis associated with potassium depletion of other causation is produced by excretion of an excess of acid in the urine, while in patients with this

* There is a sharp drop in the capacity of the tubules to reabsorb phosphate when carbonic anhydrase is inhibited with No. 6063 or when acidification is interrupted by the administration of maleate.

disorder acidification of the urine is specifically impaired.

One of the earliest noted associations of potassium depletion and alkalosis is that which occurs in some patients with Cushing's syndrome.[3,4] A similar biochemical abnormality is frequently encountered in patients treated with cortisone or ACTH[5] and has been produced experimentally in rats.[1] Presumably, depletion of body potassium produced by the salt-active adrenal steroids is the primary event. The depletion of potassium would be expected to upset the normal balance between potassium and hydrogen ions in the secretory cells of the distal tubules. Under those circumstances more acid is excreted in the urine than that necessary to maintain a normal acid-base balance and alkalosis is produced. An effect of the adrenal steroids on urine acidification in the rat is suggested by the experiments of Sartorius and Pitts.[15] It is, therefore, conceivable that the excretion of excess acid in the urine might be primary and the loss of potassium secondary to the alkalosis. This, however, is unlikely since the same picture is produced experimentally in rats by a diet simply deficient in potassium,[1,6] and since the administration of ACTH to man causes a sharp increase in the excretion of potassium but no increase in the excretion of titratable acid.[35]

Alkalosis associated with potassium depletion also occurs in a number of other situations which may or may not be associated with overactivity of the adrenals. In postoperative patients maintained largely on potassium-free fluids potassium depletion may result from continued excretion of this ion in the urine or by loss of gastrointestinal fluids.[10,36,37] The effect on acid-base balance is similar to that which occurs when the potassium deficit results from an excess of salt-active adrenal steroids. In several such instances hyperactivity of the mechanism for acidifying the urine has been strikingly demonstrated,[10,11] acid urines being excreted despite plasma bicarbonates as high as 55 mM/L. The alkalosis in these instances does not improve with and may be intensified by the administration of NaCl solutions but disappears promptly with repletion of the body potassium.[10,36,37]

Despite the fact that, for reasons discussed above and previously expressed by Mudge et al.,[26] mercurials must be considered to inhibit secretion of potassium by the renal tubules, it is a well known clinical and experimental observation that mercurial diuretics increase potassium excretion when potassium excretion previously has been low.[12] The explanation for this phenomenon has been a subject of contention and need not be discussed here.[9,26] However, the alkalosis which results from repeated administration of mercurial diuretics to patients in cardiac decompensation[38] is somewhat similar to that which occurs in the conditions already considered. In such patients there is a striking tendency to lose large amounts of potassium with each mercurial diuresis and, in some instances, the cation lost may be almost exclusively potassium.[39] Some tendency to produce alkalosis may be attributed to the loss of a fluid containing almost exclusively chloride so that bicarbonate is concentrated in the extracellular fluid that remains. However, the tendency of potassium depletion to accentuate the alkalosis by favoring exchange of hydrogen for sodium in the distal tubule with excretion of an acid urine is worthy of note.

SUMMARY AND CONCLUSIONS

Inhibition of carbonic anhydrase leads not only to loss of the capacity to acidify the urine but also produces a marked increase in potassium excretion. Since this increase can be inhibited by the administration of mercurial diuretics, it is concluded that the increased excretion of potassium is referable to increased renal tubular secretion of potassium. This phenomenon, together with the known interrelations between potassium metabolism and acid-base balance, appears to indicate that there is competition between hydrogen and potassium ions for some component of the ion exchange mechanism by which both are secreted. The physiologic and clinical implications of this competition are discussed.

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Low Potassium Syndrome Due to Defective Renal Tubular Mechanisms for Handling Potassium*

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HYPOKALEMIA, which occurs in several disease states, may be associated with characteristic findings that constitute the "low potassium syndrome." This syndrome consists of muscular weakness or paralyses, low broad T wave and a prolonged QT interval in the electrocardiogram. It responds readily to the administration of potassium salts.

The low potassium syndrome may result from: (1) decreased intake[1] or impaired absorption from the gastrointestinal tract,[2] (2) increased loss from the body either in the urine[3] or in the gastrointestinal contents,[4] or (3) an internal redistribution as in familial periodic paralysis[5] or in relation to carbohydrate metabolism.[6]

This report deals with studies in a patient who had the low potassium syndrome occurring as a complication of chronic nephritis. It has been suggested that increased potassium loss in nephritis is due to impairment of the ability of the kidney to form ammonia as a base conservation mechanism.[7,8] Evidence will be presented that the syndrome in the present instance was due to defective renal tubular mechanisms for the handling of potassium. This situation was exploited to obtain data on renal mechanisms for the excretion of potassium and to study the effects of potassium depletion and repletion on a variety of functions of the human organism.

CASE REPORT

The patient, a forty-one year old Chinese male, entered Bellevue Hospital on February 1, 1947, complaining of recurrent attacks of generalized weakness, with difficulty in walking for several days. He had come to this country twenty years before admission and had been well until a two-year visit to China ten years before admission. He then noted the beginning of a series of attacks of weakness, sometimes mild and lasting only a day or two but sometimes severe enough to prevent walking, and lasting for a week or more. Between attacks strength was normal. These intermittent attacks progressed in severity and frequency. The lower extremities were most often affected but the neck and upper extremities also frequently were involved, and many times weakness was generalized. The attacks were more frequent in winter. Moderate polydipsia, polyuria and nocturia had been noted for several years. The patient had not sought medical advice for his illness until the present admission.

His mother was said to have had similar episodes beginning at the age of forty but the patient was not clear about the details. At the age of twelve he had sudden onset of polyuria, nocturia and frequency which lasted for one year. There was no edema at this time. The patient denied all other illnesses or symptoms until the present illness.

Physical examination on admission revealed a thin, chronically ill-appearing male in no acute distress. His temperature was 99°F., pulse 80 per minute and regular, respirations 18 per

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minute and blood pressure 70/50. On standing erect the blood pressure fell to 60/30 but the patient did not lose consciousness. His weight was 101 pounds. The patient lay listlessly in bed and was unable to sit up, arise or lie down without support. His gait was slow with a paretic posture. The skin was dry and scaly. Knee and ankle jerks could not be elicited but the other deep reflexes were intact and there were no abnormal reflexes. There were hyperirritability to painful stimuli and hypotonia of the fingers. The heart size could not be made out and the cardiac sounds were faint but regular. Otherwise the physical examination was within normal limits.

Laboratory findings revealed the following: There was slight anemia with a hemoglobin of 11 gm. per cent and 3.4 million red blood cells per cubic millimeter. The leukocyte count on admission was 15,100 per cu. mm. but subsequently was within normal limits as was the differential count. The urine usually contained 2 plus protein, occasionally as much as 4 plus. Test for Bence-Jones protein was negative. There were rare red and white blood cells in the urinary sediment and from zero to many granular casts. The urine specific gravity was fixed at 1.010 on both dilution and concentration tests. The glomerular filtration rate was 43 ml./min., the renal plasma flow 298 ml./min., the filtration fraction 15 per cent and the Tm_{PAH} 21 mg./min.

Analysis of various constituents of the plasma revealed the following values during the first month: sodium 130 to 140 mEq./L., potassium 1.5 to 2.3 mEq./L., chloride 85 to 88 mEq./L., inorganic phosphorus 2.5 to 3.5 mg. per cent, calcium 10.8 to 11.2 mg. per cent, CO_2 combining power 55 vol. per cent, non-protein nitrogen 30 to 45 mg. per cent, creatinine 2.5 mg. per cent, uric acid 3.5 mg. per cent, total protein 5.9 gm. per cent, albumin 4.1 gm. per cent and globulin 1.8 gm. per cent. Oral glucose tolerance (100 gm.): fasting 111 mg. per cent, one-half hour 143 mg. per cent, one hour 154 mg. per cent, two hours 200 mg. per cent and three hours 143 mg. per cent. The BMR was +3 per cent.

X-rays of heart, lungs, skull and long bones were normal. Retrograde pyelography revealed slight dilatation of the renal pelves and calyces. There were several kinks in the upper third of the right ureter. Cystoscopy revealed a coarsely trabeculated bladder and hypertrophy of the median lobe of the prostate. During a period of weakness, the electrocardiogram showed a prolonged PR interval of 0.24 seconds, a broad notched T wave and a prolonged Q-T interval (K = 0.66). Electrocardiograms taken in the intervals between attacks showed definite regression of these abnormalities. Three electroencephalograms, two taken during periods of low potassium intake, were normal. Biopsy of the gastrocnemius muscle revealed no abnormalities.

The low plasma potassium levels associated with bouts of muscular weakness and characteristic electrocardiographic abnormalities suggested that the symptoms were part of the low potassium syndrome. This was further confirmed by the beneficial effects produced by oral administration of 46 mEq. of potassium as the citrate. The immediate response was not dramatic but the next day there was improvement in muscle strength followed shortly by complete remission of symptoms.

The urinary findings and renal function studies suggested that chronic nephritis was the cause of the hypokalemia. The etiology of the nephritis in this patient remains obscure but there is definite evidence of both glomerular and tubular damage. The diagnosis of familial periodic paralysis does not appear justified in view of the clinical course and the persistently low plasma potassium level, even when muscle strength was good. There was no evidence of gastrointestinal disturbance and the good response to oral potassium makes faulty absorption unlikely.

The patient has been followed up for three years. For seventeen months of this time he was under observation in the hospital and on diets of known composition. Each day's urine output was accurately collected and measured. Analyses of stools were not performed.

Two diets of known composition were used. Diet I furnished 2,045 calories and contained 250 gm. carbohydrate, 70 gm. protein, 85 gm. fat, 75 mEq. sodium, 92 mEq. potassium and 130 mEq. chloride. Diet II furnished 1,983 calories and contained 240 gm. carbohydrates, 60 gm. protein, 87 gm. fat, 74 mEq. sodium, 30 mEq. potassium and 71 mEq. chloride. The diets were supplemented with 0.2 gm. ferrous sulfate three times daily and 20,000 units vitamin D daily. Fluid intake was measured daily and variations in electrolyte intake were achieved by adding the requisite salts to the drinking water.

The patient cooperated willingly and exercised extreme care in following all instructions

concerning his intake and output. Except for changes induced by alterations in his potassium intake his course was uneventful. At no time did he suffer from diarrhea, nausea or vomiting. During periods of potassium depletion constipation was troublesome. The hypotension observed on admission and a definite orthostatic hypotension persisted throughout the period of observation and were unaffected by potassium intake.

Daily weights and twice daily blood pressures were obtained under fixed conditions. The following measurements were made on each twenty-four-hour urine specimen: volume, specific gravity, sodium and potassium on an internal standard flame photometer, and chloride. Qualitative determinations of protein were made frequently. For special purposes the following measurements were performed on the urine: titratable acidity, pH by glass electrode, ammonia, calcium, inorganic phosphate, creatinine and 17-ketosteroids. Twice weekly, and also whenever indicated, fasting blood samples were drawn for serum sodium and plasma potassium and chloride. Whole blood pH by the glass electrode, plasma CO_2 content and plasma inorganic phosphate, calcium, albumin and globulin, non-protein nitrogen and creatinine were determined at intervals which varied according to the purpose of the observations. Electrocardiograms and comprehensive muscle tests were made twice weekly during the first 180 days of observation and at less frequent intervals thereafter. The patient's normal muscle strength was approximately 75 per cent of the standard.

Renal functions were measured by standard clearance technics.[9] Infusions were delivered by a constant infusion pump at rates between 1 and 2 ml. per minute. Inulin and p-aminohippurate (PAH) clearances were taken as measures respectively of glomerular filtration rate (GFR) and effective renal plasma flow (PF). Tubule function was measured by the maximum rates of PAH excretion (Tm_{PAH}) and glucose reabsorption (Tm_G). At the same time sodium, potassium, chloride and inorganic phosphate were measured in the plasma and urine. This permitted calculation of the amounts of these materials that were filtered at the glomeruli, excreted in the urine and reabsorbed or excreted by the renal tubules. No corrections were made for the Donnan equilibrium nor for any possible binding on non-diffusible elements of the blood. Inulin was measured by Harrison's[10] modification of Alving, Rubin and Miller's method,[11] PAH by the Bratton-Marshall reaction[12] and glucose by Shannon's modification[13] of the Folin method.

On occasion, plasma volume by the blue dye (T-1824) method and thiocyanate space were determined.

RESULTS

It is not feasible to present all the data obtained during the studies of this patient because of the large number of determinations that were made over the period of three years. Instead, data were selected to demonstrate specific points. For orientation purposes the intake, balance and plasma levels of potassium, the estimated muscle strength and the time of renal function observations are indicated in Figure 1 for the entire period of observation. Various alterations in electrolyte intake are designated by different periods.

The plasma potassium level was almost always below the lower limit of normal. Although the level varied directly with the intake, there were many and considerable fluctuations without apparent explanation.

Several periods (v, xi, xvi) represent times when the patient was at home reporting to the clinic for observation. Diet was not controlled during these periods. During period xvi the patient was maintained on 20 gm. of potassium citrate daily. He gained 27 pounds in this time and felt better than at any other period of observation.

Effects of Variations of Electrolyte Intake on Potassium Balance. The effect of variations in potassium intake was studied on several occasions (Fig. 1, periods ii, iii, iv, vii, viii, ix, x). Reduction of potassium intake to 30 mEq. daily (periods ii, iii, vii) resulted in a prompt, considerable and sustained negative potassium balance and a fall in plasma potassium to levels well below 2 mEq. per L., eventually reaching the neighborhood of 1 mEq. per L. Even when the daily potassium intake was 104 mEq., an amount within the range furnished by ordinary diets, there was a distinct tendency for a negative balance and the plasma level was rarely over 2 mEq. per L. (periods i,

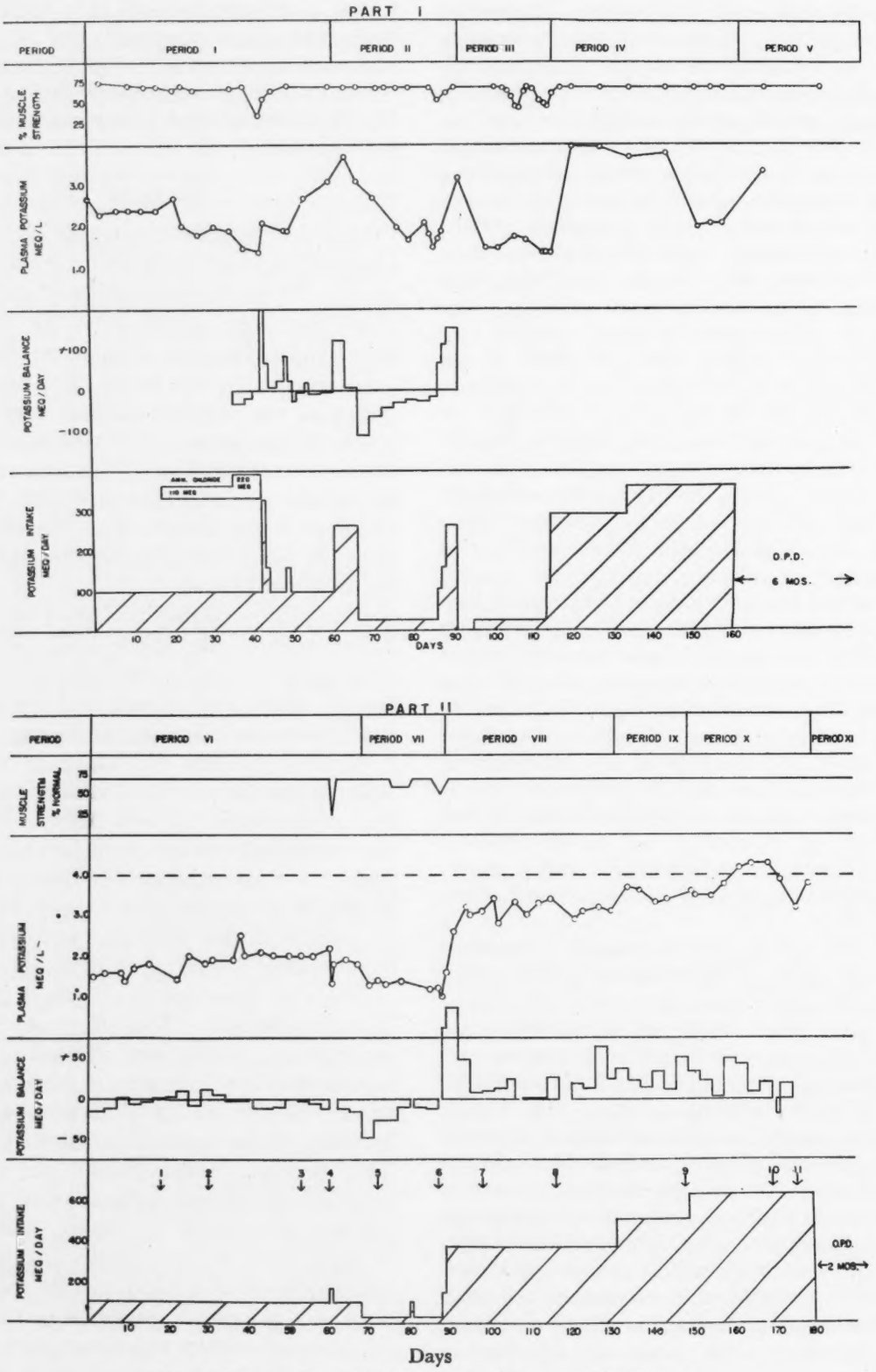

FIG. 1. Parts I and II. See legend opposite page under Part III.

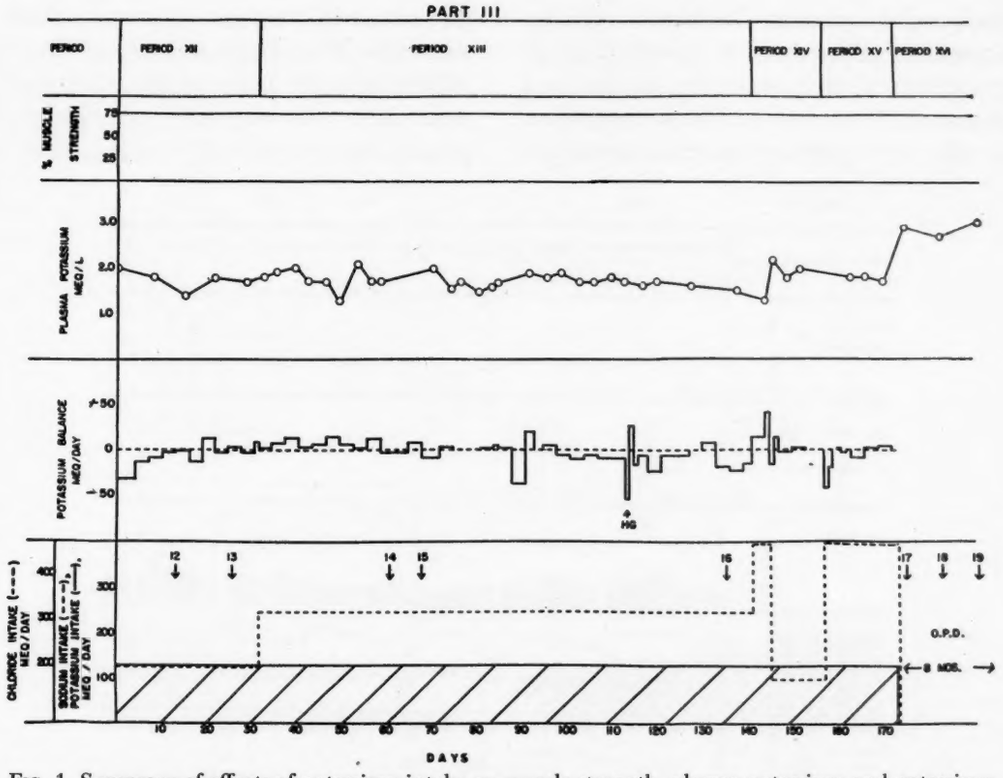

FIG. 1. Summary of effects of potassium intake on muscle strength, plasma potassium and potassium balance during three years of observation. Muscle strength during part I was quantitated at the times indicated by the open circles but was only roughly estimated during parts II and III. Note that the scales for potassium balance and potassium intake vary in the different parts. In part III the scales for the electrolyte intakes are so adjusted that both sodium and chloride can be indicated by the broken line. Arrows indicate when renal function studies were performed, the numbers corresponding with the experiment numbers in Table I.

VI, XII, XIII, XIV, XV). Positive balance* was observed as soon as greater amounts of potassium were administered (periods I, II, IV, VIII, IX, X). The plasma potassium level also rose promptly although even on the highest dosage (625 mEq. daily) it rarely exceeded 3.5 mEq. per L., the lower limit of normal. The persistence of a positive potassium balance up to ninety days following institution of high intake (periods VIII, IX, X) indicates the extensive depletion previously suffered.

Detailed data obtained over a period of 180 days, corresponding to periods VI to X of Figure 1, are presented in Figure 2. Potassium intake was varied between 30 and 625 mEq. daily. In addition to the relation of potassium balance and plasma level to potassium intake, weight, 17-ketosteroid excretion and plasma chloride were all directly related to the potassium chloride intake. These changes will be discussed further in a subsequent section.

In general, there was a reciprocal relation between sodium and potassium balance as the potassium intake was varied. (Fig. 3.) Chloride balance appeared to be related to the sum of the sodium and potassium balance in that chloride was retained when base was retained and vice versa.

When sodium chloride intake was varied and the potassium intake was kept constant (periods XII, XIII, XIV, XV), there were few if any changes in potassium plasma levels or excretion rate. Detailed data obtained during this period are shown in Figure 4.

* Stools were not analyzed for potassium content but it is unlikely that fecal loss of potassium was sufficient to alter to a significant degree the markedly positive balances.

The reciprocal relation between sodium and potassium balance noted earlier (Fig. 3) during variations in potassium intake was not apparent. Moreover, serum sodium and chloride did not approach normal until the tassium and sodium balances when potassium intake was varied suggests that sodium moves into the cells as they are depleted of potassium. As the cells are repleted with potassium on a high intake, the sodium

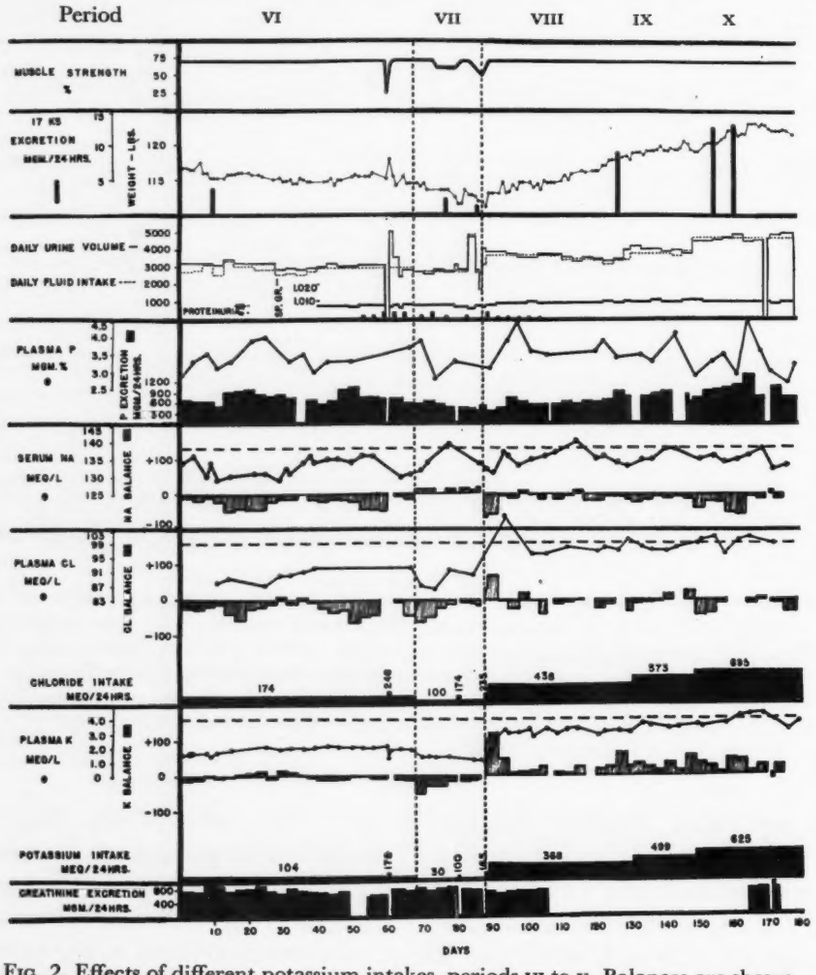

FIG. 2. Effects of different potassium intakes, periods VI to X. Balances are shown in mEq. per day.

sodium chloride intake was increased to 325 mEq. daily. (Fig. 4.)

Comment on Electrolyte Balances: The direct relationship between intake of potassium and its plasma level and renal excretion is suggestive although not conclusive evidence that the hypokalemia in this patient was due to renal loss. Likewise, the amount of sodium required to achieve a positive sodium balance and to raise the serum sodium level indicates that the patient also had an element of "salt-losing" nephritis.[14]

The reciprocal relationship between potassium moves out into the extracellular fluid and subsequently is excreted by the kidneys.

The converse, however, does not appear to hold. Potassium balance is not affected by sodium intake even though considerable sodium depletion may be present. This is not surprising in view of the chiefly extracellular position of sodium and the relatively unimportant contribution of potassium to the total osmotic pattern of the extracellular compartment.

Effect of a Metabolically Alkaline Potassium Salt. The effect of a high alkaline potas-

sium salt intake of as much as 239 mEq. of potassium daily, 212 mEq. in the form of the citrate, is indicated in Figure 5. The plasma CO_2 combining power rose as high as 75 vol. per cent (34 mm. per L.) and against alkalosis. Little or no ammonia was present in the urine during alkalosis. The sodium balance showed no consistent trend.

Comment: Hypokalemia is sometimes attributed to alkalosis. However, in spite of

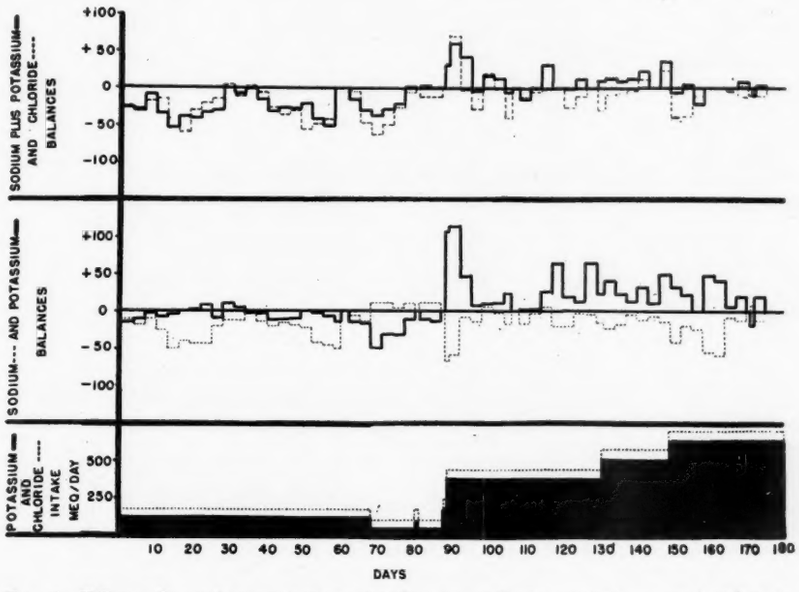

FIG. 3. Effect of varying potassium intakes on sodium, potassium and chloride balances. Balances are shown in mEq. per day. Note the inverse relation between potassium and sodium balances.

urinary pH values increased almost to 8. The alkalosis, however, was compensated in that these were only minor variations in blood pH. The usual direct relationship between potassium intake, balance and plasma levels was apparent.

Chloride excretion decreased and chloride balance (not shown in the figure) became strongly positive during the administration of potassium citrate. On both occasions there was a rise in plasma chloride of almost 10 mEq. per L. Chloride excretion no longer more or less balanced the sum of sodium and potassium excretion. Instead, decreased excretion of ammonia and titratable acidity along with increased urinary pH represented the kidneys' defense against the alkalosis. The negative values for ammonia plus hydrogen ion during potassium citrate administration shown in Figure 5 represent the back-titration of the alkaline urines to pH 7.4 with 0.1 N HCl. This is, in effect, a measure of the kidneys' defense renal disease this patient's kidneys were able to adjust successfully to a large dose of a metabolically alkaline salt. At the same time the increased potassium intake resulted in the usual positive potassium balance.

Effect of Potassium Intake on Other Electrolytes, Body Weight, Glomerular Filtration Rate and 17-ketosteroid Excretion. Variations in the intake of potassium produced changes in other electrolytes. (Fig. 2.) Thus plasma chloride level is also directly related to potassium chloride intake although this was presumably the result of the increased chloride intake. Considerable fluctuation in serum sodium and plasma inorganic phosphate were observed but they bore no particular relationship to potassium intake. Phosphate excretion seemed to be reduced during the low intake period but creatinine excretion was not affected. Calcium excretion (data not shown) was not affected by potassium intake. The fluid intake and output data reflect the degree of accuracy

exercised by the patient in consuming his allotted fluids and in collecting his urine. Body weight, glomerular filtration rate and plasma potassium level all varied directly with the potassium intake in a striking fashion. (Fig. 6.) The 17-ketosteroid also varied directly with the potassium intake.

Effect of Potassium Intake on Muscular and Nervous Functions. Over prolonged periods of time there was only a rough correlation between the plasma level of potassium and muscle strength. The plasma potassium level sometimes fell below 1.5 mEq. per L. with no observed decrease in muscle strength. Occasionally bouts of weakness developed with no change in the plasma level. Muscle weakness developed usually when body stores of potassium were apparently severely depleted rather than in relation to its plasma concentration.

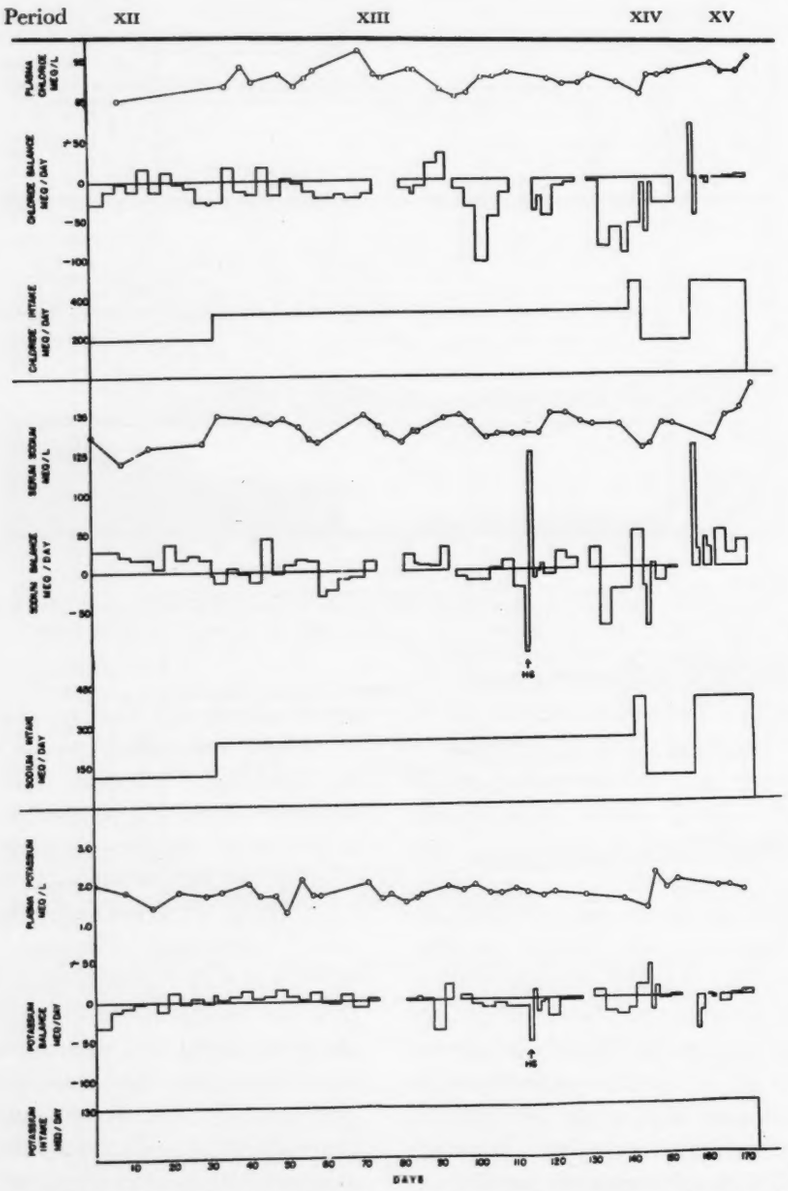

FIG. 4. Effect of variations in sodium and potassium intakes on plasma levels and balances of sodium, potassium and chloride, periods XII to XV. Hg = 1 ml. mercupurin I.M.

Seven bouts of moderate to severe muscular weakness were observed. All were produced by design. Five occurred following low potassium feeding, one as a result of ammonium chloride administration and one following a hypertonic glucose infusion. All bouts responded to administration of potassium. Two bouts could be classified as severe, the other five as moderate. In the two severe bouts all muscle groups tested showed decreased strength and there was little if any difference between the two sides of the body. In the moderate bouts of weakness some muscle groups were affected while others were normal. The muscles of the lower extremities, back and hips were usually affected while the upper extremities, scapular, neck and facial muscles were usually spared. In one bout the small muscles of the hand were affected along with the hips, back and lower extremities.

Deep tendon reflexes were usually hypoactive but were variable and showed no particular relationship to potassium intake or plasma levels. Periods of potassium depletion were characterized by three findings which may be attributed to involvement of the autonomic nervous system. Thus every time low potassium intake was instituted troublesome constipation, bladder atony and prolongation of the P-R interval in the electrocardiogram developed. These abnormalities regressed promptly on administration of potassium.

Effect of Potassium Depletion on the Heart. Disturbances in cardiac electrical potentials were regularly observed during potassium depletion and were similar to those described by many authors as characteristic of the low potassium syndrome. (Fig. 7.) They consisted of broadening and flattening of the T wave, prolongation of the Q-T interval (K = 0.66) and changes in the character of the S-T segment. These characteristic findings always developed during the potassium deprivation or loss, and were noted before and independently of the appearance of muscular weakness. Although abnormalities in the cardiac electrical potentials occurred *only* in the presence of hypokalemia, their extent from day to day bore no close relation to the level of plasma potassium. Further, normal electrocardiograms were observed at times

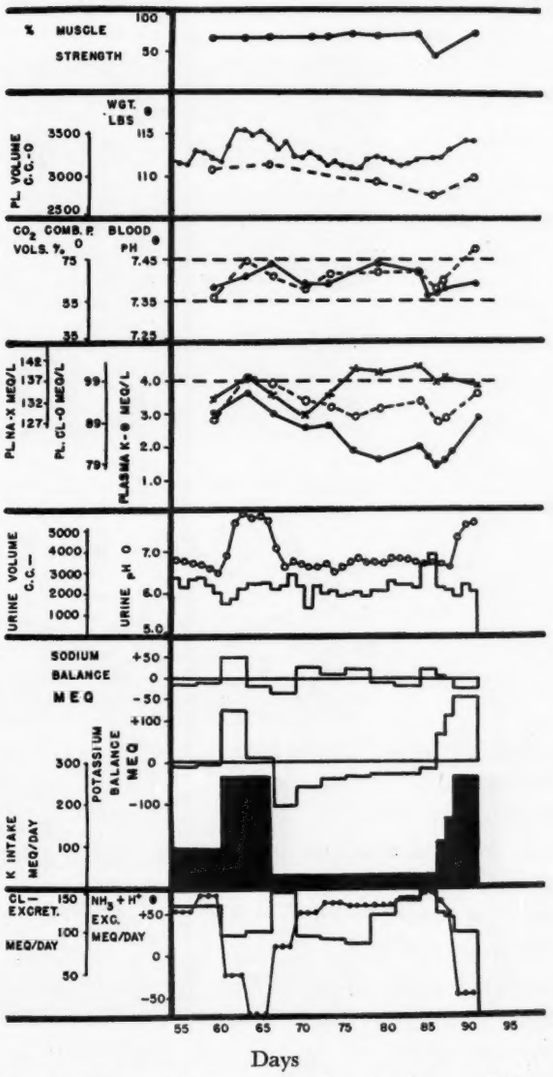

FIG. 5. Effects of different potassium intakes, period II. The extra potassium administered before and after the period of low potassium intake was given chiefly as the alkaline salt, potassium citrate.

in the presence of moderate hypokalemia. Thus the electrocardiogram was not a precise indicator of the degree of hypokalemia.

In contrast to the correlation between plasma potassium level and the electrocardiogram on a day-to-day basis the acute effect of potassium administered during the depleted state was striking. As shown in

Figure 8 the height of the T wave was directly proportional to the changes in plasma potassium level following individual doses of potassium chloride.

During periods of potassium depletion the electrocardiogram also showed an increasing degree of A-V block with a prolonged P-R interval and dropped beats. These changes were observed only when the patient was in the recumbent position and could be abolished by assuming an erect posture or by the intravenous injection of 3 mg. atropine. (Fig. 7.) Atropine had no effect on the T wave and S-T segment abnormalities. The A-V block therefore appears to be an effect of potassium depletion on relative vagal control.

Comment: Potassium depletion affected the heart in two ways: (1) an effect on the muscle cell indicated by the prolongation, flattening and broadening of the T wave and (2) a neurogenic effect indicated by readily reversible increased vagal tone. These effects could be separated by releasing vagal control, as with atropine. The height of the T wave of the electrocardiogram could be correlated with the plasma potassium level in acute experiments after potassium administration. However, in the day to day changes correlation was poor.

Differential Effects of Potassium on Skeletal and Cardiac Muscle Function. Although the muscular paresis and electrocardiographic abnormalities of the low potassium syndrome both responded to the administration of potassium salts, the responses occurred at different rates. (Fig. 8.) During a bout of weakness 1 gm. of potassium chloride was given intravenously followed by oral doses of 5 gm. approximately four hours later and by 10 gm. the next day. Each dose of potassium chloride resulted in a sharp rise in plasma potassium and chloride concentration followed by a progressive fall. No significant changes were noted in serum sodium, pH or CO_2 combining power. Muscle strength increased progressively, being almost 75 per cent (normal for this patient) at forty-eight hours.

On two occasions during potassium therapy for bouts of weakness directly recorded skeletal muscle potentials were independent of the changing plasma potassium levels whereas the T wave of the electrocardiogram followed them closely.

Comment: It appears that potassium ad-

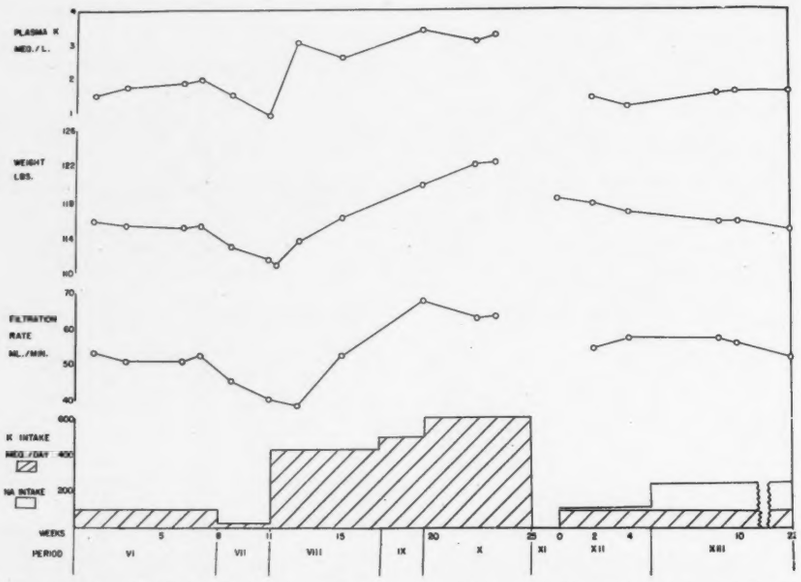

FIG. 6. Effect of variations in sodium and potassium intakes on plasma potassium level, body weight and glomerular filtration rate. Note lack of effect of increasing the daily sodium intake from 74 mEq. during periods VI to X to 120 mEq. in period XII and then to 220 mEq. in period XIII.

ministered to the depleted subject is rapidly distributed to the heart, as judged by the rapid changes in the T wave of the electrocardiogram. This is followed by redistribution of potassium to other tissues as evidenced by the gradual but steady increase in muscle strength over the subsequent forty-eight-hour period. In contrast, the height of the T wave of the electrocardiogram repeatedly reflected the acute changes in plasma potassium level following each administration of potassium. The increases in T wave height were quite transient so that they had returned almost to the control value at a time when muscle strength was showing continuous improvement. (Fig. 8.)

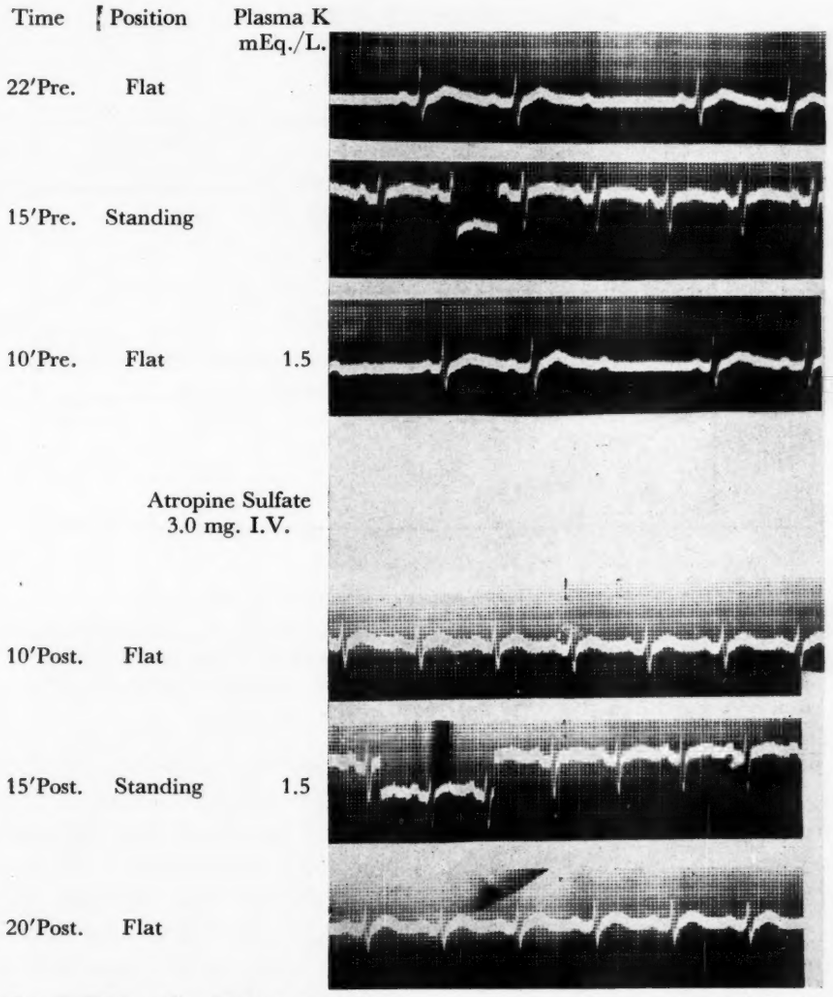

FIG. 7. Effect of position and atropine on the electrocardiogram (lead II) during potassium depletion. Partial heart block present in the recumbent position is abolished by standing and by atropine. These procedures did not alter the characteristic T wave and Q-T interval changes of hypokalemia.

The hypothesis that potassium is distributed to different tissues at different rates is subject to question since it is based on observation of electrical potentials in the case of the heart and of strength in the case of skeletal muscle. Nevertheless the independence of the directly recorded skeletal muscle potentials from changing plasma potassium levels and from cardiac electrical potentials is compatible with the hypothesis.

RENAL MECHANISMS

The ready production of negative potassium balance by a low intake and its correction by a high intake suggested that hypokalemia in this instance was due to

excessive renal loss of potassium. This mechanism was further suggested by the finding of relatively high concentrations of potassium in the urine at times when its concentration in the plasma was low. Thus high urinary potassium concentrations (as high as 92 mEq./L.) were not uncommon when the plasma level was below 2 mEq./L. On one occasion when the plasma potassium was 1.4 mEq. per L. the urine potassium concentration was 41 mEq. per L. and 79 μEq. of potassium were being excreted each minute.

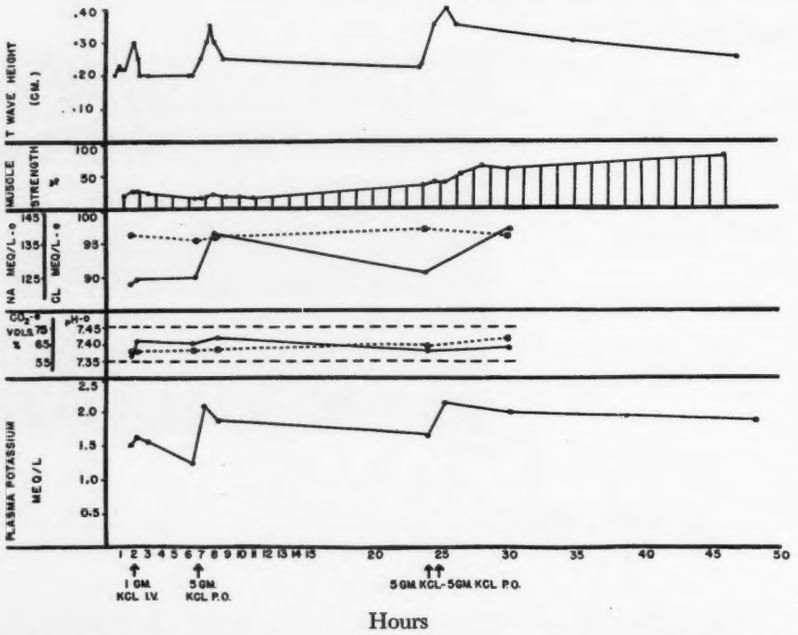

FIG. 8. Effect of potassium on height of T wave of the electrocardiogram and on skeletal muscle strength. The T wave increased in height as the plasma potassium rose after each dose of potassium. In contrast, muscle strength showed a gradual increase over forty-eight hours.

Pattern of Renal Function. Shortly after admission, while the patient was depleted of potassium, renal function determinations revealed a moderate degree of impairment. The glomerular filtration rate was 43 ml. per minute, the renal plasma flow 298 ml. per minute and the Tm_{PAH} 21 mg. per minute. Corresponding normal values for male subjects, corrected to the surface area of the patient, are 124 ml., 666 ml. and 74 mg. per minute.[9] Subsequent renal function studies (Table 1) revealed approximately the same degree of impairment. The renal plasma flow varied between 294 and 394 ml. per minute and the filtration fraction between 14 and 19 per cent on five occasions. On one occasion the renal plasma flow was 175 ml. per minute. The maximum capacity for tabular excretion of PAH varied between 32 and 36 mg. per minute on four occasions and the maximum capacity for reabsorption of glucose varied between 159 and 182 mg. per minute on six occasions. Variations in daily potassium intake between 104 and 625 mEq. had no obvious effect on these functions. The glomerular filtration rate, however, varied directly with the potassium intake* as did the body weight and presumably the volume of extracellular fluid. (Fig. 6.) The filtration rate fell as low as 41 ml. per minute after nineteen days on the low potassium intake (30 mEq. daily) and rose as high as 68 ml. per minute on the high intake. Although glomerular filtration rate generally varied with the potassium intake, the relationship

* Variation of filtration rate with potassium intake has been noted in another patient with chronic glomerulonephritis.

was not a precise one and, curiously, the lowest filtration rate of 39 ml. per minute was observed nine days after changing from the low to the high intake.

These observations indicate moderate impairment of both glomerular and tubular functions but give no clue concerning etiology. Glomerular filtration rate, but not the other renal functions, seemed to vary directly with the potassium intake. The mechanism responsible for the effect of potassium intake on glomerular filtration rate is not readily apparent.

TABLE I

ELECTROLYTE EXCRETION STUDIES

Experiment No.*	Potassium Intake (mEq./da.)	Period†	Glomerular Filtration Rate (ml./min.)	Potassium				Sodium Excreted	Chloride Excreted	Inorganic Phosphate Excreted (mg./min.)
				Plasma (mEq./L.)	Filtered (μEq./min.)	Excreted (μEq./min.)	Excreted (Per cent)	(μEq./min.)		
1	104	Control	54.7	1.52	83	24	28	23	22	0.68
2	104	Control	51.5	1.77	91	49	53	59	73	0.54
		74 mEq. potassium	50.3	2.87‡	124	45	37	59	50	0.67
3	104	Control	50.9	1.87	95	62	66	72	76	....
		Tm_{PAH}	51.6	1.88	97	104	109	352	155	....
4	104	Control	53.0	1.81	96	31	33	8	7	0.66
		Tm_G	64.7	1.60	104	190	183	1,080	1,138	1.12
5	30	Control	45.5	1.44	65	23	35	31	23	0.82
6	30	Control	41.2	1.03	42	21	50	36	35	0.61
7	438	Control	39.2	3.06	121	159	132	42	370	0.49
8	438	Control	52.8	2.59	136	150	111	20	160	0.36
		74 mEq. potassium	59.1	3.78‡	214	261	122	102	336	0.54
9	499	Control	68.0	3.40	231	191	82	18	201	0.40
10	625	Control	63.4	3.14	200	309	154	46	380	0.12
		Tm_G	85.8	2.53	216	550	254	1,537	2,153	0.77
11	625	Control	63.7	3.13	199	308	155	57	327	0.76
		Tm_{PAH}	59.4	2.82	168	327	196	118	263	1.22
12	104	Control	55.6	1.50	77	79	102	58	97	0.63
		Tm_{PAH}	47.1	1.40	67	115	172	203	121	0.65
13	104	Control	59.2	1.43	85	77	91	25	59	0.66
		Tm_G	65.3	1.29	85	161	189	447	546	0.90
14	104	Control	59	1.63	96	67	70	61	55	0.85
		Tm_{PAH}	50.6	1.37	69	125	178	233	133	0.67
15	104	Control	53.4	1.64	88	71	81	122	134	0.76
		Tm_G	61.0	1.34	82	143	174	478	604	1.13
16	104	Control	48.3	1.72	84	35	42	23	.....	0.41
		Tm_G	60.6	1.60	97	163	168	602	.....	0.91
17	104	Control	57.5	2.89	166	88	52	78	.....	0.44
		Tm_G	68.0	2.61	179	175	100	719	.....	0.90
18	196	Control	52.1	2.74	152	131	86	12	114	0.38
		Tm_G	91.1	2.17	197	330	167	1,012	1,385	0.82
19	196	Control	63.9	3.00	194	175	92	99	120	0.38
		Tm_G	76.5	2.90	229	258	113	903	1,047	0.72

* Experiment numbers correspond with those of Figure 1.

† Electrolyte excretions are indicated for both control periods and periods during which Tm_{PAH} and Tm_G were measured.

‡ Peak plasma potassium level.

It has been shown recently that alkalosis *per se* can cause reduction in renal function which may require a number of months to

return toward normal.[15] Although hypokalemia is frequently associated with alkalosis, there is no evidence that the present patient was in alkalosis. He gave no history of vomiting and the blood CO_2 was usually between 25 and 27 mEq. per L. The blood

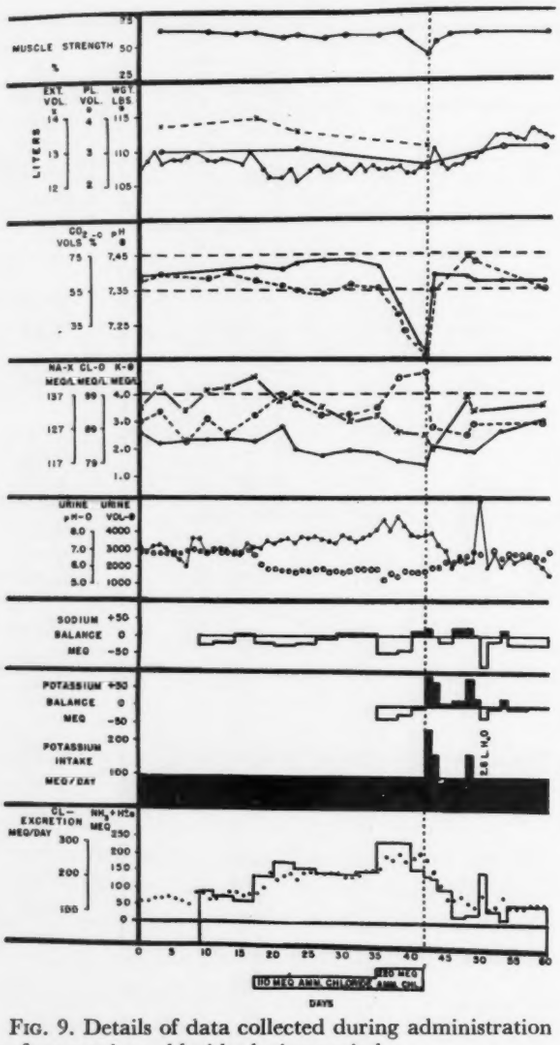

FIG. 9. Details of data collected during administration of ammonium chloride during period 1.

pH was approximately 7.40 and the urine pH was generally below 7.00. Finally, the patient was able to defend adequately against alkalosis when as much as 212 mEq. of potassium citrate was administered each day. (Fig. 5.) For these reasons it does not appear likely that this patient's reduction in renal function was secondary to alkalosis.

Potassium Loss Not Due to Impaired Renal Base Conservation Mechanisms. The patient was in normal acid-base balance, as evidenced by normal blood pH and alkali reserve, while on the regular ward diet and while on Diet 1. Titratable acidity and ammonia appeared in the urine in normal amounts. To test the ability of the kidneys to manufacture ammonia and to adjust to acidosis, 110 mEq. ammonium chloride was administered daily while on Diet 1. (Period 1, Fig. 1.) The detailed data are shown in Figures 9 and 10, and represent a fairly normal response. During the first nine days of ammonium chloride administration there were slight decreases in alkali reserve, serum sodium and plasma potassium, along with a negative sodium balance and presumably a negative potassium balance. The plasma chloride rose almost to normal. However, within one day (Figs. 9 and 10) the excretion of ammonia and titratable acidity began to increase. After nine days the renal defense was completely successful in that the increased chloride excretion was now balanced by increased amounts of urinary ammonia and titratable acidity. There was no further fixed base deficit and the blood electrolytes remained constant.

When the daily dose of ammonium chloride was increased to 220 mEq., there was a further rise in the excretion of ammonia plus titratable acidity in the urine which, however, was not sufficient to compensate for the greatly increased chloride excretion. Progressive acidosis and diminution in alkali reserve resulted. There was again a negative sodium balance and a negative potassium balance as well. By the seventh day of the increased intake the blood pH had fallen to 7.19, the CO_2 content to 13 mm./L., the serum sodium to 125 mEq./L. and the plasma potassium to 1.4 mEq./L. The electrocardiogram revealed 2:1 heart block, prolonged Q-T interval, broad low T waves and an occasional premature contraction of ventricular origin. The patient suffered a severe attack of muscular paralysis but improved rapidly after the oral administration of 141 mEq. potassium citrate. In subsequent experiments similar improve-

ment resulted from the use of potassium chloride.

There was little if any impairment of the ability of this patient's kidneys to manufacture ammonia or to excrete an acid urine. Although increased potassium excretion When the potassium intake was decreased to 30 mEq. daily, the per cent excretion of potassium remained high (Experiments 5 and 6) although the plasma level fell to as low as 1.03 mEq. per L. Urine potassium concentrations as high as 92 mEq. per L.

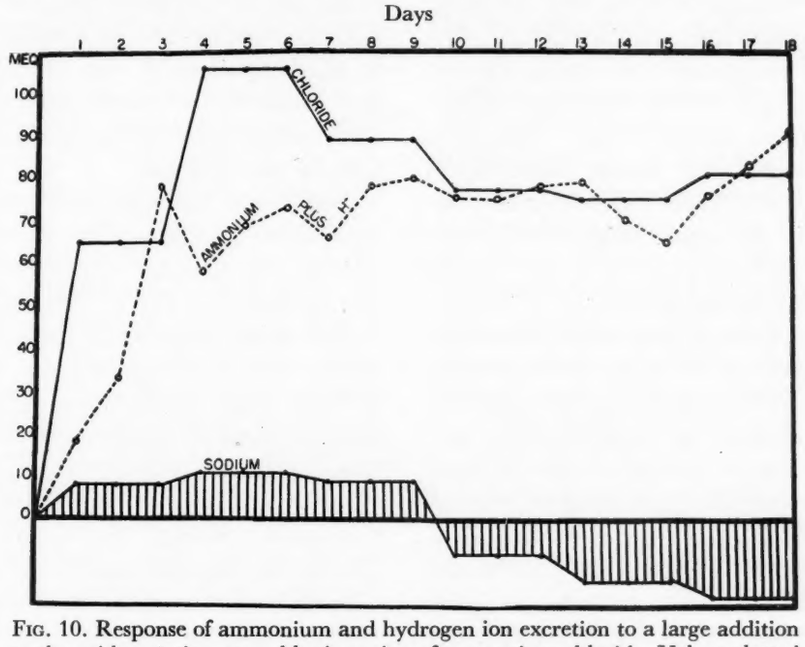

FIG. 10. Response of ammonium and hydrogen ion excretion to a large addition to the acid excretion caused by ingestion of ammonium chloride. Values plotted are increments over levels before ammonium chloride.

could be induced by acidosis, very large amounts of ammonium chloride were required to achieve this result. Thus inability to defend against acidosis was a most unlikely cause for the considerable potassium depletion and hypokalemia observed in this patient on ordinary diet.

Observations on Excretion of Potassium and Other Electrolytes by the Kidneys. Potassium: Data on electrolyte excretion by the patient while on various potassium intakes are summarized in Table 1. Normal persons on normal diets and under ordinary circumstances rarely excrete in the urine more than 20 per cent of the amount of potassium filtered at the glomeruli.[16] This patient, however, on a normal daily potassium intake of 104 mEq. excreted between 28 and 102 per cent of the filtered load (Experiments 1 to 4, 12 to 16) even though the plasma potassium level was very low, ranging between 1.43 and 1.87 mEq. per L. were observed when the plasma level was below 2 mEq. per L.

When the daily oral intake of potassium was increased over 400 mEq. (Experiments 7 to 11, Table 1), potassium excreted in the urine exceeded the amount filtered at the glomeruli in four of the five observations. In Experiments 10 and 11 the "per cent excretions" of potassium were 154 and 155, respectively. Data such as these can be explained only on the basis of excretion of potassium by the renal tubules. Potassium excretion in the urine did not exceed the amount filtered during Experiments 18 and 19 although the patient was on a high potassium intake at home.

The aforementioned observations were obtained with the patient lying flat in bed. The effect of his postural hypotension on electrolyte excretion is not known. However, estimations were made of the amounts of potassium filtered, excreted in the urine and

reabsorbed or excreted by the tubule cells throughout twenty-four-hour periods. Twenty-four-hour endogenous creatinine clearances, corrected for creatinine to inulin clearance ratios determined three times during the period of these observations, were utilized to approximate the average filtration rate. During the period of the highest potassium intake (625 mEq. daily) but not during periods of average intake more potassium appeared in the urine per twenty-four hours than could have been accounted for by filtration. Thus excretion of potassium by the renal tubules was evident under conditions of ordinary ward activity of an ambulant patient.

Potassium excretion in the urine following a single oral dose of 74 mEq. was greatly modified by the status of the patient's stores of potassium. Following such a dose, administered during a period of low intake (Table 1, Experiment 2), potassium excretion in the urine fell from 49 to 45 μEq. per minute while the filtered load increased from 91 to 124 μEq. per minute and the per cent excretion fell from 53 to 37. In contrast, during a period of high potassium intake and at a time when more potassium was in the urine than could be accounted for by filtration alone (Experiment 8), a dose of 74 mEq. was followed by an increase in urinary potassium excretion from 150 to 261 μEq. per minute, and an increase in its per cent excretion from 111 to 122. In both experiments a comparable rise in plasma potassium of slightly more than 1 mEq. per L. occurred. The filtration rate did not change in Experiment 2 and rose only slightly in Experiment 8. Parenthetically, it might be noted that excretion of potassium by the tubule cells is not solely dependent on the plasma potassium level, urine flow or filtration rate.

Potassium excretion was greatly increased by loads of PAH or glucose administered intravenously for Tm measurements. Such experiments during periods of average potassium intake uncovered the phenomenon of renal tubular excretion of potassium in seven or eight instances (Table 1, Experiments 3, 4, 12 to 17). During a glucose infusion in Experiment 10, while the patient was on a high potassium intake, potassium excretion reached the excessive rate of 0.5 mEq. per minute. Potassium in the urine exceeded the amount filtered by two and a half fold while the clearance of potassium in this experiment was as high as 218 ml. per minute, a value which represented approximately two-thirds of the renal plasma flow of this patient.

Sodium and Chloride: Sodium and chloride excretion in the urine increased greatly during the glucose experiments (Table 1, Experiments 4, 10, 13, 15 to 19). Although the absolute increase in the amount of these electrolytes excreted in the urine was far greater than the increase in potassium excretion, their excretion by the renal tubules could not be demonstrated. Urine sodium excretion, like that of potassium, was also increased during the PAH experiments (Table 1, Experiments 3, 11, 12 and 14). Chloride excretion, however, increased relatively less than did sodium excretion, and in Experiment 11 actually decreased.

Phosphate and Calcium: Phosphate excretion was variable and more or less paralleled the plasma phosphate level. (Table 1.) The per cent of filtered phosphate that was excreted in the urine was generally between 25 and 40, with extremes of 18 and 51, values somewhat above normal. The calculated amount reabsorbed showed only moderate variations. Excretion of phosphate and calcium (data not shown), like the other electrolytes, increased during the glucose and PAH infusions but excretion by the tubules could not be demonstrated.

Ammonia and Titratable Acidity: The excretion of ammonia and titratable acidity was measured during the first five studies on high potassium intakes (Experiments 7 to 10). Ammonia excretion increased from 18 to almost 50 μEq. per minute as the daily potassium chloride dosage was increased, indicating once more that there was no particular defect in the ability of this

patient's kidneys to respond in the usual fashion to an excess load of acid (chloride).

In normal subjects under usual conditions the amount of potassium excreted in the urine represents less than 15 per cent of the amount filtered at the glomeruli, and rarely exceeds 20 per cent.[16] Most of the filtered potassium, therefore, is reabsorbed by the tubules. Recently, however, excretion of potassium by the renal tubules of dog[17] and normal man[18] has been demonstrated. When large amounts of potassium were administered intravenously, more potassium was found in the urine than could be accounted for by glomerular filtration alone. Moreover, renal tubular excretion of potassium during forced diuresis has been shown in the dog.[19]

Patients with nephritis and reduced glomerular filtration rates tend to excrete in the urine abnormally high percentages of filtered potassium.[16,20] Such an excretion is essential if potassium balance and a normal potassium concentration in the body fluids are to be maintained in the presence of unchanged intake and reduced filtration rate. One report[20] indicates that in patients with terminal renal disease the amount of potassium in the urine may exceed the amount filtered. Filtration rate, however, was estimated from the endogenous creatinine clearance.

The present patient had renal disease and excreted in the urine as much as 50 per cent of the filtered potassium when he was on a low potassium intake and at times as much as 88 per cent when on an average intake. Moreover, tubular excretion of potassium was easily demonstrable either by increasing the daily potassium intake or by infusions of glucose or PAH during periods of average intake. This excessive loss of potassium could not be attributed to inability of the kidneys to defend against acidosis or alkalosis. Although the filtration rate was moderately reduced, this patient excreted a higher percentage of his filtered potassium than did other nephritics with comparable filtration rates.[16] These facts, together with high excretion of potassium in the urine in the face of extremely low plasma potassium levels, point to a defective renal tubular mechanism for the handling of potassium.

Reduced tubular reabsorption of potassium could account for some of the increased urinary excretion of potassium. However, there are several observations which are most easily explained by increased tubular excretion of potassium. Thus in Experiment 2 of Table 1, performed during a period of average potassium intake, the 53 per cent urinary excretion of filtered potassium during the control period represents excessive loss. Nevertheless the tubules were capable of absorbing considerably more potassium, as evidenced by no change in potassium excretion in the urine as the filtered load increased from 91 to 124 μEq. per minute following an oral dose of potassium. A similar experiment performed during a period of high potassium intake (Experiment 8, Table 1) revealed a greater increase in potassium excretion in the urine than in the amount filtered. Barring the unlikely possibility of a decrease in tubular reabsorption of potassium, increased tubular excretion is a likely basis for these findings. The considerable excess of urinary potassium over that contained in the glomerular filtrates in Experiments 7, 10 and 11 is most reasonably explained by increased tubular excretion rather than by decreased absorption of potassium. Likewise, decreased tubular absorption of potassium is a possible but unlikely explanation to account entirely for the great increases in urinary potassium excretion occasioned by glucose infusions (Table 1, especially Experiment 10)

In summary, then, it appears that this patient's hypokalemia is due to a defect of unknown etiology involving the renal tubular mechanisms for handling potassium. Decreased tubular reabsorption and increased tubular excretion probably both play a role. Excretion of potassium by the tubules was easily demonstrable. Whether constitutional, hormonal or cellular dehydration play any role in this defect or

whether the defect is due entirely to the direct effects of disease on the renal tubules is not clear. In any case this instance of potassium-losing nephritis is distinct in its mechanism from those previously described.[7,8]

SUMMARY

Prolonged observations were made on the characteristics and the mechanism of production of the low potassium syndrome in a forty-two year old Chinese male with nephritis of unknown etiology. The syndrome consisted of intermittent bouts of muscular weakness, atony of the bladder, constipation and electrocardiographic changes of a broad flattened T wave, prolonged Q-T interval, prolonged P-R interval and dropped beats, all associated with low serum potassium levels.

The plasma potassium level varied between 1.5 and 2.3 mEq./L. when the patient was on a regular diet (104 mEq. potassium daily), fell as low as 1 mEq./L. on a low potassium intake (30 mEq. potassium daily) and rarely exceeded 4 mEq./L. even when the potassium intake was six times greater than normal (625 mEq. potassium daily). The potassium balance was negative on an average potassium intake and became positive only when the daily potassium intake was increased to 425 mEq. or more.

In general the serum sodium levels were low and sodium balance tended to be negative except when sodium intake was high. A reciprocal relationship between the potassium and sodium balances was apparent when the potassium intake was varied. Variations in sodium intake and balance, however, were not attended by reciprocal changes in the potassium balance.

The plasma chloride level was usually low and chloride balance appeared to be related to the sum of the sodium and potassium balance in that chloride was retained when base was retained and vice versa.

Potassium depletion appeared to affect adversely muscle strength and the vegetative nervous system. The severity of signs and symptoms referable to these systems varied in the presence of a constant plasma potassium level; nor was development of symptoms inevitable at any particular plasma potassium level. The height of the T wave of the electrocardiogram could be correlated with the plasma potassium level in acute experiments after potassium administration. Although electrocardiographic abnormalities occurred only during periods of potassium depletion, the day-to-day correlation between the height of the T wave and plasma potassium levels was poor.

Glomerular filtration rate, renal plasma flow and maximum capacities of the renal tubules to excrete p-aminohippurate and to reabsorb glucose were approximately one-third of normal. The rate of glomerular filtration, but not the other functions, varied directly although not precisely with the level of daily potassium intake. During periods of low potassium intake and in spite of very low plasma potassium levels the kidneys continued to excrete urine containing appreciable amounts of potassium. Loss of potassium in the urine was not due to inability of the kidneys to defend by the usual mechanisms against either alkalosis or acidosis.

Under conditions of low potassium intake as much as 50 per cent of the potassium filtered at the glomeruli appeared in the urine (normal = less than 20 per cent). Tubular excretion of potassium was easily demonstrable whenever the patient was on a high potassium intake. Potassium given during a period of potassium depletion and at a time when an abnormal amount was being lost in the urine demonstrated that the tubules were capable of reabsorbing additional potassium. A similar experiment performed during a period of high potassium intake resulted in a greater increase in the amount of potassium in the urine than in the glomerular filtrate.

It is probable that both decreased absorption and increased excretion of potassium were a part of the renal tubular defect

responsible for the excessive loss of potassium in the urine.

Acknowledgments: The authors are indebted to Dr. Henry Kohn, Dr. Paul Reidel and Miss Harriet Heffernan for their assistance in carrying out many of the observations. The authors are also indebted to Dr. Joseph W. Jailer for the determinations of 17-ketosteroids in the case reported. The muscle tests were performed by the Department of Physical Medicine.

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Renal Tubular Acidosis with Osteomalacia*

Report of Three Cases

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THE recent definition of osteomalacia secondary to chronic renal acidosis as a clinical entity has contributed considerably to the understanding of metabolic bone disease. Its dramatic response to therapy is of major importance. This syndrome was first described by Butler, Wilson and Farber[1] in 1936. More extensive studies of its pathogenesis and treatment were subsequently reported by Albright and his group.[2–4] Recent papers have brought the total number of reported cases to fourteen[5–11] and the present authors have been informed of six other unpublished instances of this disorder.

Renal tubular acidosis‡ with osteomalacia has been diagnosed in three patients at the Presbyterian Hospital during the past two years. The present report describes certain studies which confirm and extend the previous observations of other investigators.

CASE REPORTS

CASE I. W. D., Unit No. 860620, a forty-nine year old Negro dry cleaner, was first admitted in 1939 for treatment of a urethrocutaneous fistula which had developed following instrumentation at another hospital. Bacillus proteus was reported in the urine cultures and the patient received sulfanilamide. In 1941 a bilateral ureterosigmoidostomy was performed following which the patient was asymptomatic until 1945. At this time repeated episodes of left renal colic occurred in association with chills and fever; on each occasion these symptoms readily responded to sulfadiazine. Intravenous pyelography in 1946, however, revealed bilateral impairment of dye excretion and left hydro-ureter and hydronephrosis.

Pains in the arms, legs and chest and weakness of the lower extremities appeared during the summer of 1946. These symptoms increased during the ensuing months until in January, 1947, the patient was unable to walk without assistance. There was an associated weight loss of 20 pounds. Analysis of the serum at this time disclosed low carbon dioxide combining power and inorganic phosphorus, a normal calcium level and slightly elevated urea nitrogen and alkaline phosphatase values. X-rays revealed mild generalized demineralization but no renal calcification; intravenous pyelograms showed the presence of right hydronephrosis.

In an effort to relieve the pain the patient took 9 gm. of salicylates daily for a period of two weeks at the end of which he was admitted in stupor resulting from acute salicylate poisoning. Following recovery from this acute episode the findings included a normal blood pressure, direct and indirect tenderness over the upper third of both femora and the right twelfth rib, overactive tendon reflexes and fascicular twitching of the muscles of the lower extremities. Weakness and mild atrophy of the thigh and calf muscles were also observed. There was a marked disturbance of gait characterized by a shifting of the trunk from side to side with each step.

Laboratory studies revealed a mild hypochromic anemia. The urine, obtained by rectal tube, was alkaline to litmus, had a specific gravity of 1.012 and contained ++ albumin. No reducing substances were found. Phenolsulfonphthalein excretion was 25 per cent in

‡ The term "renal tubular acidosis" will be used for brevity instead of "renal acidosis resulting from tubular insufficiency without glomerular insufficiency" suggested by Albright and his associates.

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185 cc. in two hours. Serum values were as follows: albumin 5.1 and globulin 2.2 gm. per 100 cc., bicarbonate 12.7 mEq./L., chloride 113.7 and potassium 3.0 mEq./L. The serum non-protein nitrogen was 29, calcium 10.3 and inorganic phosphorus 1.3 mg. per cent, and the alkaline phosphatase 7.3 Bodansky units per 100 cc. X-ray studies disclosed linear decalcifications in the right twelfth rib and the right scapula in addition to the earlier findings. Electromyograms and chronaxie studies were normal.

The diagnosis of osteomalacia secondary to renal tubular acidosis was made and the patient was transferred to the metabolism ward for a limited study. As shown in Table 1 the patient retained a considerable amount of potassium and lost chloride during administration of a mixture of potassium acetate, bicarbonate and citrate.

Following discharge he was given 10 gm. of sodium bicarbonate, 50,000 units of vitamin D and 1.5 gm. of sulfadiazine daily and was placed on a high calcium diet. At the end of one week serum levels were: carbon dioxide content 27.3, sodium 140, potassium 4.9 and chloride 102.4 mEq./L. One month later all pain had disappeared and the gait disturbance had improved markedly.

The patient was followed up for nineteen months during which time his visits to the outpatient department were irregular and he took inadequate doses of alkali. Nevertheless, symptoms recurred only on one occasion. No skeletal recalcification was observed on x-ray after treatment for eighteen months.

Case II. E. P., Unit No. 808705, a twenty-eight year old unmarried white salesgirl, was admitted in December, 1945, with a two-month story of right renal colic associated with the passage of urinary calculi. In the past she had had frequent sore throats but had received no known chemotherapy. In 1939 she suffered a traumatic fracture of the right hip which healed uneventfully. Physical examination revealed no abnormality other than brownish pigmentation of the skin of both legs. Laboratory studies disclosed minimal albuminuria, a serum calcium of 9.3, inorganic phosphorus of 2.3 and urea nitrogen of 14 mg. per 100 cc. The serum alkaline phosphatase was 5.3 Bodansky units per 100 cc. On oral doses of 4 gm. of ammonium chloride daily the urine pH did not fall below 6.4. During one twenty-four-hour period the calcium balance was found to be negative; the intake was 277 mg., the urinary output 423 mg. Analysis of a stone showed calcium phosphate. Urine cultures were negative. Mild skeletal demineralization and bilateral nephrocalcinosis were found on x-ray.

Muscular weakness and pains in the back and extremities appeared early in 1946. A provisional diagnosis of parathyroid adenoma was made and the patient was readmitted for exploration. At this time hemolytic Escherichia coli and non-hemolytic streptococci were found in a urine culture. At operation the parathyroid glands were described as enlarged but no adenoma was found.

In May, 1947, the x-rays were reviewed by Dr. Marjorie Le May who made the diagnosis of Milkman's syndrome (osteomalacia with pseudofractures). Shortly thereafter serum analyses were found to be compatible with osteomalacia secondary to renal tubular acidosis and the patient was admitted to the metabolism ward for further investigation.

On this admission the urine contained no albumin and concentrated to 1.011. Phenolsulfonphthalein excretion was 60 per cent in 820 cc. in two hours. Serum values were as follows: sodium 133, potassium 2.7, carbon dioxide content 12.9 and chloride 115 mEq./L.; calcium 9.3, inorganic phosphorus 3.5 and urea nitrogen 16 mg. per cent. The alkaline phosphatase was 5.5 Bodansky units per 100 cc. The pH of venous blood taken without stasis was 7.25. In addition to previous findings numerous ribbon-like areas of decalcification were observed on x-ray. Because of the appearance of fresh petechial hemorrhages in the skin of the legs studies of the blood-clotting mechanism were made with negative results. A skin biopsy, obtained at a later date, was interpreted as showing the presence of Majocchi's disease, a localized dermatologic disorder of unknown etiology.

The patient was discharged on a regimen identical to that prescribed for Case 1, except for a larger dose of sodium bicarbonate. At a routine clinic visit two months later the patient was symptom-free and volunteered that she felt stronger than at any time during the previous ten years. Although x-rays taken seven months after the beginning of treatment showed no change in the degree of demineralization, most of the pseudofractures had recalcified completely. The patient was seen most recently in October, 1950, one year after an uncomplicated

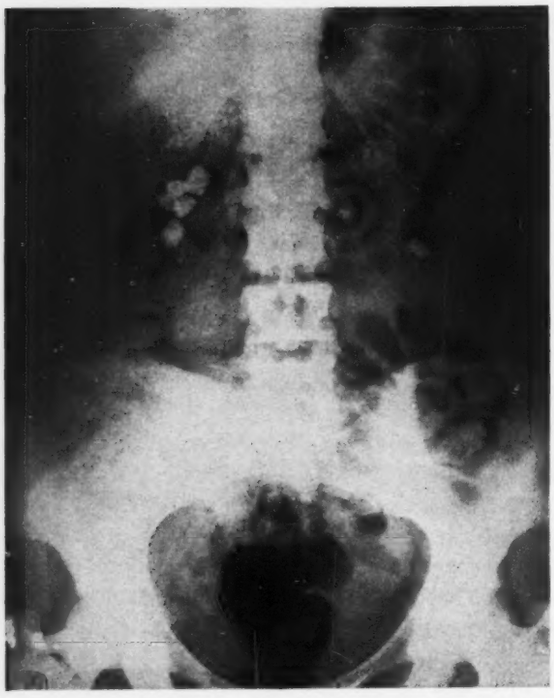


FIG. 1. Case III. X-ray of the kidneys taken in 1947 shows calculi and nephrocalcinosis.

pregnancy. Treatment with sodium bicarbonate and vitamin D had been continued and there had been no recurrence of symptoms. At this time the serum findings were normal and x-rays showed disappearance of the previously noted pseudofractures as well as a definite decrease in demineralization. There was no significant change in the degree of renal calcification.

CASE III. M. G., Unit No. 884608, a twenty-eight year old white housewife, was referred to the Presbyterian Hospital in September, 1947, with a seven-year history of recurrent renal colic. Shortly prior to the delivery of her first child in 1940 the patient had received 22 gm. of neoprontosil during an eight-day period for treatment of a peritonsillar abscess. One month after an uneventful delivery she experienced the first attack of bilateral flank pain. After several recurrences of this pain an appendicectomy was performed without relief. The symptoms subsided gradually but returned following delivery of her second child in 1942. At this time an exploratory laparotomy failed to reveal any abnormality. In 1943 the patient passed five pea-sized stones in the urine and a subsequent x-ray was said to have shown "both kidneys loaded with stones."

Muscular weakness, polydipsia and polyuria appeared during 1943 and 1944. The symptoms became considerably worse during two months on a restricted calcium intake but responded favorably to treatment with vitamins A and D which were given intermittently during the following two years. In 1946, however, the patient began to experience bone pains and increasing weakness. A "rolling" gait developed early in 1947. The family history included diabetes mellitus in a brother and half-brother.

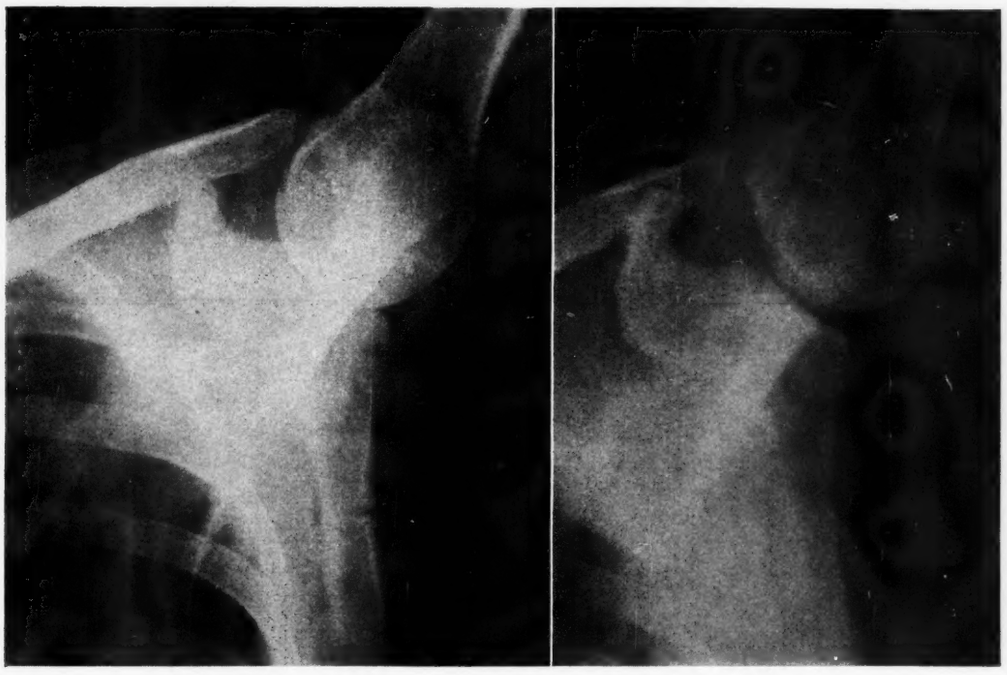
On physical examination tenderness to palpation was noted in the upper abdomen, in both costovertebral angles and over both hips and the pubic symphysis. The urine was alkaline to litmus and had a maximum specific gravity of 1.018. Tests for albumin and glucose were negative. Phenolsulfonphthalein excretion was 33 per cent in two hours. Ureteral cultures yielded Esch. coli and hemolytic staphylococcus aureus. The twenty-four-hour excretion of 17-ketosteroids was 5.3 mg. and urinary amino acid excretion was within normal limits.* Analysis of the blood disclosed the following values: sodium 136.2, potassium 2.6, bicarbonate 11.1 and chloride 106 mEq./L.; calcium 10.3, inorganic phosphorus 2.4 and urea nitrogen 18 mg. per 100 cc. The serum alkaline phosphatase was 6.9 Bodansky units per 100 cc. and the arterial blood pH was 7.28.

Bilateral renal calculi and diffuse calcification in the renal areas were seen on x-ray. Intravenous pyelography revealed poor dye excretion and mild bilateral hydronephrosis. Several pseudofractures were found but there was no generalized skeletal demineralization. The x-rays of the kidneys and of a pseudofracture of the scapula before and after treatment are reproduced in Figs. 1 and 2.

The patient was transferred to the metabolism ward and was given a low calcium diet. She became rapidly weaker and at the end of forty-eight hours was unable to move her head, arms or legs or to turn in bed. There was no gross involvement of the extra-ocular, facial, intercostal muscles or the diaphragm, nor were any cardiovascular disturbances observed. The serum potassium was 2.5 mEq./L. and the muscle potassium concentration was reduced.[12] Chronaxie studies† disclosed definite decreases in the excitability of all muscles tested including those of the face.

* Kindly determined by Dr. N. Young of the Memorial Hospital, New York, N. Y.

† We are indebted to Dr. Joseph Moldaver of the Department of Neurology for these measurements.



2A 2B

FIG. 2. Case III. X-rays of the left scapula show the presence of a pseudofracture (A) in October, 1947, and its disappearance (B) in May, 1949, nineteen months following the institution of treatment.

An electrocardiogram showed depression of S-T segments. The symptoms were considered a manifestation of acute potassium deficiency and a saline infusion containing 60 mEq. of potassium was administered. There was a dramatic return of muscle strength following the infusion although the serum potassium had risen only to 2.9 mEq./L. At a later date the electrocardiogram and muscle excitability were found to be normal. The diet was supplemented with 40 mEq. (3 gm.) of potassium chloride daily and the balance study was completed without further incident.

Following discharge the patient was maintained on a daily dose of 71 mEq. (6 gm.) of sodium bicarbonate as well as vitamin D and a high calcium diet. All symptoms other than transient attacks of ureteral colic disappeared within six weeks after the start of treatment. Skeletal x-rays taken a year later showed complete healing of the pseudofractures without any change in the renal calcification. A significant weight gain (23 pounds) was observed in this patient as in the others and was ascribed in part to increased appetite following relief of the acidosis. The patient's third pregnancy, in 1949, was characterized by episodes of renal colic of increased frequency and severity; these were sometimes associated with fever and were treated with penicillin, sulfadiazine and sulfacetamide. The patient was delivered uneventfully of a normal child in September, 1949. Renal function studies were performed one week and six months following delivery.

METHODS

Balance studies were carried out on the metabolism ward. In Case I observations were limited to a single three-day period during which a constant diet and 30 mEq. daily of added alkali were given. A constant diet was provided in Cases II and III for five three-day periods of which the first two were control. Sodium acetate (85 and 100 mEq. per day, respectively) was administered orally during the final three periods of each of these studies. Determinations of the dietary intake were based upon analysis of the homogenized diet for a twenty-four-hour period. The dietary intake in Case II was corrected for uneaten residues which were analyzed. Stool determinations are reported as averages for the first two and the last three periods, respectively. A small sample of urine was collected before break-

fast each morning for pH measurement (glass electrode).

The following chemical determinations were carried out: sodium and potassium, by internal standard flame photometry,[13] carbon dioxide content,[14] chloride,[15] calcium,[16] inorganic phosphorus,[17] magnesium,[18] total serum protein[19] and total nitrogen by the micro-Kjeldahl technic. Renal function, measured in Cases II and III by accepted clearance methods,[20–22] was studied by Dr. Stanley E. Bradley.

TABLE IA
METABOLIC DATA

Case No.	Period*	Sodium (mEq./day)				Potassium (mEq./day)				Calcium (mg./day)			
		Intake	Output		Balance	Intake	Output		Balance	Intake	Output		Balance
			Urine	Stool			Urine	Stool			Urine	Stool	
I†	..	69.8	64.3		+ 5.5	105	80		+25	...	...	...	.....
II	1‡	78	54	13	+11	57	64	7	−14	562	192	189	+181
	2‡	78	64	13	+ 1	57	62	7	−12	562	239	189	+134
	3§	120	94	3	+23	37	40	7	−10	470	101	376	− 7
	4§	163	122	3	+38	53	37	7	+ 9	531	104	376	+ 51
	5§	163	133	3	+27	53	34	7	+12	545	111	376	+ 58
III	1‡	64	88	4	−28	87	65	12	+10	208	245	175	−212
	2‡	64	62	4	− 2	87	67	12	+ 8	208	192	175	−159
	3§	164	91	4	+69	87	68	10	+ 9	208	132	227	−151
	4§	164	134	4	+26	87	53	10	+24	208	156	227	−175
	5§	164	137	4	+23	87	50	10	+27	208	144	227	−163

* Periods were three days in length.
† Data were collected during the first three days of alkali therapy only.
‡ Control period.
§ During administration of alkali.

RESULTS

Balance Studies. The findings are listed in Tables IA, B and II. All patients retained potassium during treatment with alkali; the patients in Cases II and III, treated for nine days, went into positive sodium and water balance as well. The sharp decrease in the rate of phosphorus loss was striking. There were no consistent alterations in the over-all balance of calcium and only minimal variations were observed in the chloride and magnesium balances. The nitrogen balance in Case III became positive during treatment. The changes in the potassium, phosphate and nitrogen balances resulted almost entirely from decreases in the urinary output of these substances. Similar reductions were observed in the urinary excretion of calcium and magnesium but these were offset by a coincidental increase in stool values. As shown in Table II the serum concentrations of bicarbonate and chloride returned to or toward normal in all cases. The serum sodium levels rose in Cases II and III. The serum calcium failed to rise significantly in these patients. A slight fall in the level of inorganic phosphorus in the serum was observed in Case III, and a decrease in total serum protein in all. The urine pH rose uniformly during the treatment periods.

Renal Function Studies. Clearance measurements are summarized in Table III. It is evident that the filtration rate (mannitol clearance) was only moderately reduced in both patients and that the renal plasma flow (PAH clearance) was essentially normal when the tubular defects were marked. The

glucose Tm was at the lower limit of normal in Case II and definitely decreased in Case III. Marked reduction of Tm_{PAH} and Tm diodrast was also observed in Case III. Slight but progressive impairment of kidney function was found in this patient following muscular function,[24] renal calculi and chronic acidosis with mild dehydration. Analysis of the blood serum reveals hyperchloremic acidosis usually accompanied with reduced concentrations of inorganic phosphate and potassium. The levels of

TABLE IB
METABOLIC DATA (*continued*)

Case No.	Period*	Magnesium (mg./day)				Chloride (mEq./day)				Phosphorus (mg./day)				Nitrogen (gm./day)			
		Intake	Output		Balance	Intake	Output		Balance	Intake‖	Output		Balance	Intake	Output		Balance
			Urine	Stool			Urine	Stool			Urine**	Stool‖			Urine	Stool	
I†	...	...	...	...	....	69	111		−42	....	....	...	.....	13.26	11.43		+1.7
II	1‡	186	65	81	+40	68.4	57.8	0.4	+10.2	1070	1110	180	−220	11.86	9.11	0.88	+1.8
	2‡	186	69	81	+36	68.4	72.1	0.4	− 4.1	1070	1340	180	−450	11.86	9.25	0.88	+1.7
	3§	138	32	124	−18	24.4	62.7	0.6	−38.9	757	552	407	−202	8.46	8.52	1.33	−1.3
	4§	175	51	124	0	63.4	59.8	0.6	+ 3.0	978	582	407	− 11	11.26	8.90	1.33	+1.0
	5§	181	57	124	0	64.3	60.8	0.6	+ 2.9	997	593	407	− 3	11.29	8.37	1.33	+1.5
III	1‡	...	...	...	....	105	107	4.8	− 6.8	674	591	220	−137	9.32	8.24	1.27	−0.1
	2‡	...	...	...	....	105	82.4	4.8	+17.8	674	554	220	−100	9.32	8.24	1.27	−0.1
	3§	...	...	...	....	105	92.6	0.9	+11.5	674	471	265	− 62	9.32	8.75	1.19	−0.6
	4§	...	...	...	....	105	102	0.9	+ 2.1	674	435	265	− 26	9.32	6.63	1.19	+1.5
	5§	...	...	...	....	105	94.6	0.9	+ 9.5	674	395	265	+ 14	9.32	5.94	1.19	+2.1

* Footnotes as in Table IA.
‖ Total phoshorus.
** Inorganic phoshorus.

her third pregnancy. These findings are in essential agreement with previous reports[2,23] and indicate that the disturbance of the renal base-conserving mechanisms may occur in the absence of major alterations of renal hemodynamics.

Tissue Analyses. Muscle biopsies, obtained prior to therapy, were analyzed for sodium, potassium, chloride and nitrogen. In all three patients a significant decrease in the intracellular concentration of potassium was associated with an increase in the calculated intracellular sodium. These findings have been described elsewhere in detail.[12]

COMMENTS

The findings in seventeen patients with osteomalacia resulting from renal tubular acidosis, including the patients in the present study, have been summarized in Tables IV and V. The sex incidence is predominantly female; only four cases have been described in males. In general the symptomatology is referable to osteomalacia, altered neuro-

serum sodium, calcium and non-protein nitrogen are as a rule within normal limits. The elevation of the alkaline phosphatase is associated with osteomalacia demonstrable by x-ray. In contrast to the expected finding in acidosis the urine pH is generally above 6.0 and the urinary output of ammonium ion is submaximal.[3] Radiologic findings include renal calculi, nephrocalcinosis and pseudofractures, with or without generalized skeletal demineralization.

Few anatomic studies are available. In two autopsied cases[3,7] extensive tubular damage was described. Calcification was limited for the most part to the collecting tubules, pyramids and the renal pelvis. Parathyroid hyperplasia was found in one patient,[3] and enlargement of these glands in another (Case II of the present series). No evidence of parathyroid abnormality was found at necropsy in five infants with an apparently similar renal disorder, but in these patients there was no associated osteomalacia.[1,25]

Albright and his associates[3,4] suggest that the characteristic disturbances are attributable to a reduction in the capacity of the renal tubular base-sparing mechanisms permitting the loss of fixed base, particularly calcium and potassium. In their view a resulting tendency toward hypocalcemia (counteracted by a mobilization of calcium from bone) produces, through parathyroid stimulation, hyperphosphaturia and hypophosphatemia. According to these investigators alkali therapy prevents the tendency toward hypocalcemia and thus its sequelae. The decreased urinary phosphate excretion following treatment in the present studies was not accompanied with any significant change in the serum calcium level. Although this does not exclude a secondary alteration in the level of parathyroid activity, relief of the acidosis *per se* may conceivably play an important role.

Because the major portion of fixed base filtered at the glomerulus is sodium, impairment of the renal mechanisms for conservation of base might be expected to result predominantly in the urinary loss of this ion. The retention of sodium and water and elevation of the serum sodium concentration observed during alkali therapy in Cases II and III suggest that antecedent mild sodium and water depletion may have occurred. Marked hyponatremia and car-

TABLE II

SERUM VALUES* DURING BALANCE STUDIES SUMMARIZED IN TABLES IA AND B

Case No.	Period	Sodium (mEq./L.)	Potassium (mEq./L.)	Calcium (mg. %)	Magnesium (mg. %)	Bicarbonate (mEq./L.)	Chloride (mEq./L.)	Inorganic Phosphorus (mg. %)	Hematocrit (%)	Total Protein (%)	Body Weight (kg.)
I	1‡	136.9	3.7	...	...	13.5	116.8	...	45.9	7.5	60.3
		136.2	3.9	...	...	18.3	109.0	...	46.0	7.3	59.9
II	1†	132.5	2.8	8.3	2.3	14.0	.....	3.1	....	...	41.2
			2.9	8.3	2.4	14.3	117.5	2.3	....	...	....
	2†	134.8	2.9	...	...	12.8	114.2	...	39.8	7.9	41.0
	3‡	137.8	2.7	8.2	2.3	19.3	105.4	2.5	....	...	40.6
	4‡	139.0	2.7	...	...	20.8	109.3	...	....	...	41.3
	5‡	139.5	2.9	8.5	2.3	22.4	106.8	2.5	40.0	7.3	41.7
III	1†	134.0	3.2	9.3	...	....	116.5	2.1	52.0	7.1	50.7
	2†	132.4	3.2	9.1	...	10.4	112.5	2.5	....	6.9	50.4
	3‡	138.5	2.9	9.0	...	19.3	105.8	2.0	....	7.0	50.9
	4‡	138.6	2.8	9.3	...	24.7	103.4	1.8	....	6.1	51.7
	5‡	141.8	3.2	9.3	...	27.3	103.1	1.7	44.3	6.3	52.2

* Determinations were made at the end of the corresponding period. Where two values are listed, the first was obtained at the beginning of the period.

† Control period.

‡ Treatment period (during administration of alkali).

TABLE III

RENAL FUNCTION STUDIES*

	Normal† Women	Case II	Case III		
			1/28/48	9/27/49‡	3/13/50§
Effective renal plasma flow (cc. per min.)	594 ± 102	503	396	294	222
Effective renal blood flow (cc. per min.)	982 ± 184	758	555‖ 548 768‖	485	382
Glomerular filtration rate (cc. per min.)	117 ± 15	65	69	70	30
Filtration fraction	.202 ± .031	.141	.173	.223	.126
Tm_{PAH} (mg. per min.)	77.5 ± 12.9	....	13.2	....	....
Tm diodrast (mg. per min.)	42.6 ± 9.5	....	.....	23.0	16.3
Tm glucose (mg. per min.)	303 ± 55	245	139	208	166
PAH extraction ratio	0.935	....	0.713	....	....

* Corrected to 1.73 m^2 surface area.

† Values from Smith,[20] Bradley[21] and Chasis et al.[22]

‡ One week following delivery.

§ Six months following delivery.

‖ Corrected for the reduced PAH extraction ratio.

diovascular collapse, however, have not been reported in adult patients with this disorder. The discovery of a renal tubular mechanism for the secretion of potassium,[26,27] which appears to conserve sodium by ion exchange[28] and is believed to operate in response to dehydration,[29] offers a possible explanation for the selective loss of potassium in the place of sodium.

The occurrence of hyperchloremia has not been fully explained. In accordance with suggestions made previously[2,7] one might speculate that this results at least in part from a degree of hemoconcentration

TABLE IV

SYMPTOMS AND X-RAY FINDINGS IN SEVENTEEN CASES OF RENAL TUBULAR ACIDOSIS WITH OSTEOMALACIA

Case No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15*	16†	17‡	No. of Cases
Reference	1	2	5	3, 6	7	3	3	3	3	3	8	9	10	11	..	..	..	..
Sex	M	F	F	M	F	F	F	F	F	F	F	M	F	F	M	F	F	..
Age	10	13	15	40	29	40	17	28	18	23	11	44	49	19	47	28	28	..
Symptoms																		
Bone pain	..	..	..	+	..	+	+	..	+	+	..	..	+	..	+	+	+	9
Weakness	+	..	+	+	..	..	..	+	..	+	..	+	+	..	+	+	+	10
Gait disturbance	..	+	+	..	..	+	+	..	+	+	..	..	+	..	+	+	+	10
Polyuria	+	..	+	..	+	..	..	+	+	..	..	+	..	+	..	+	+	9
Polydipsia	+	..	+	..	+	..	..	..	..	..	..	+	..	..	..	+	+	6
Renal colic	..	..	..	..	+	..	..	+	+	..	..	..	..	+	..	+	+	6
X-ray																		
Pseudofractures	..	..	..	0	0	+	+	0	+	+	..	+	+	+	+	+	+	10
Demineralization	+	+	+	0	0	+	+	0	+	0	+	0	+	+	+	+	0	11
Renal calculi	+	+	+	+	+	0	0	+	+	+	+	0	..	+	0	+	+	12
Nephrocalcinosis	+	+	+	+	+	0	0	+	+	0	+	+	..	+	0	+	+	12

* Case I of the present series.
† Case II of the present series.
‡ Case III of the present series.

TABLE V

LABORATORY FINDINGS* IN SEVENTEEN CASES OF RENAL TUBULAR ACIDOSIS WITH OSTEOMALACIA

Case No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	Mean
Serum																		
Non-protein nitrogen mg. %	†	21	45	24	32	16	33	16	16	28	22‡	16§	22	19§	28	14§	18§	25.6
CO_2 mEq./L.	16	19	11	18.8	14.3	16.9	17.8	18	13.8	20	15.7	11.8	23	11.8	12.7	12.9	11.1	15.6
Chloride mEq./L.	124	121	126	110	113	107.8	111	117	115.6	117	116	116	118	111.8	113.7	115	116.5	115.8
Sodium mEq./L.	.....	.....	.....	141	150	138.8	.....	139	138	145	.....	140	166	.....	137.8	133	136.2	142.3
Potassium mEq./L.	.....	.....	.....	2.5	.....	.....	.....	.....	.....	.....	.....	.....	2.3	.....	3.0	2.7	2.5	2.6
Calcium mg. %	†	9	9	8.8	11	9.5	11.2	9.7	10.4	9.7	10.2	9	7.6	8.7	10.3	8.3	9.1	9.5
Phosphorus mg. %	**	1.9	2.7	2.7	1.8	1.9	2.2	2.2	1.9	2.8	3.1	1.8	4.7	3.4	1.3	2.3	2.2	2.5
Alkaline phosphatase B. U. %	1.0††	22.6	.....	5.5	13§§	7.5	16.3	4.8	21	9.2	30.6‡‡	9‡‡	23	8.2	7.3	5.5	7.2	11.5
Total protein gm. %	.....	6.5	....	6	9.5	6.9	8	6.6	7.1	8.6	.....	7.8	7.1	6.1	7.3	8.1	7.8	7.4
Urine																		
Specific gravity (maximum)	1.009	1.010	1.018	1.018	1.007	1.018	1.028	1.010	1.008	1.012	1.006	1.012	.....	1.007	1.012	1.011	1.018	.....
pH (lowest recorded)	.....	6.5	Alk.	6.5	6.6	5.5	5.5	.....	.....	.....	Alk.	7	.....	8	Alk.	6.8	6.9	.....
Albumin	+	+	+	+	+	+	+	+	+	+	+	+	.....	+	+	+	+	.....
Glucose	.....	0	0	0	0	?	.....	.....	0	.....	.....	0	.....	0	0	0	0	.....
PSP excretion (hr.)	2	1	2	2		2	1	1	1	.....	.....	2	.....	2	2	2	2	
%	70	45	45	80	.....	28	35	40	50	.....	.....	40	.....	25	25	60	33	.....
Culture	.....	0	.....	+	0	+	0	+	0	0	.....	0	.....	+	+	+	+	.....

* Maximum deviations from normal unless otherwise noted.
† "Normal."
‡ Urea.
§ Urea nitrogen.
** "Reduced."
†† Kay units (normal = 0.3).
‡‡ King-Armstrong units (normal = 15).
§§ Jenner-Kay units (normal = 6).

proportional to the loss of extracellular sodium but in excess of the chloride loss. In two of the presently reported balance studies treatment was accompanied with retention of sodium and water as well as a rapid decrease in the serum chloride concentration. In one of these patients the reduction of serum chloride occurred despite a concomitant positive chloride balance.

Finally the decrease in the urinary excretion of nitrogen during treatment with alkali, a finding which has also been reported previously,[3] may in part reflect reduced ammonia production by the kidney as well as a possible decrease in protein catabolism in response to correction of the acidosis.[30]

Although the pathogenesis of renal tubular acidosis has been clarified to some extent,[3] its etiology remains obscure. A congenital defect may account for some cases. The possible role of pyelonephritis has been suggested by Albright and his associates who reported its presence in one autopsied case. This hypothesis is supported by the development of the disorder in Case 1 of the present series five years after bilateral ureterocolostomy and in association with evidence of urinary infection, stasis and impairment of renal function. Results of clearance studies are compatible with this view. Cases of hyperchloremic acidosis following bilateral ureterocolostomy have been observed by Waterhouse,[31] Leight and Perlmutter,[32] and Ferris and Odell who reviewed a large series of patients after this type of surgery.[33] The latter authors suggest that the electrolyte disturbance results from the absorption of chloride from the urine during its passage through the colon. This attractive theory may well account for the serum changes occurring during the early postoperative period, particularly when associated with nitrogen retention which usually distinguishes these cases from those with renal tubular acidosis. Greenspan[9] has mentioned the possibility that renal tubular damage following sulfonamide therapy may be an etiologic factor. The onset of the disorder in at least seven of the reported cases, however, preceded the introduction of the sulfonamide compounds into clinical medicine.

The regimen of alkali and vitamin D therapy advocated by Albright and his collaborators has been described elsewhere in detail.[3,4] It has been uniformly successful in producing rapid symptomatic improvement and in correcting the abnormal serum electrolyte pattern. In several cases x-ray studies have shown a complete or partial disappearance of the osteomalacia as well as a reduction in the number of renal calculi. Frequent determinations of serum bicarbonate levels have facilitated the initial regulation of the alkali intake which may then be maintained for long periods with only occasional checks. Serum calcium levels have been followed at regular intervals to avoid the danger of vitamin D toxicity although this is believed to be minimal with the dose employed. Vitamin D has been discontinued following disappearance of the bone lesions. If sodium and water retention become a problem owing to advancing renal disease or intercurrent cardiac failure, the use of a low sodium diet and substitution of potassium bicarbonate for varying amounts of the sodium salt may be of value.

SUMMARY

Three new cases of renal tubular acidosis are described and the findings in fourteen previously reported cases are summarized. Renal function studies were performed in two patients. Balance studies revealed decreased excretion of inorganic phosphate, retention of sodium, potassium and water, and variable changes in the chloride balance following the initiation of treatment with alkali.

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Clinical Recognition of Pyelonephritis, with a New Stain for Urinary Sediments*

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A NUMBER of methods for staining urinary sediments have been described. They can be divided into two groups: one in which the sediment is dried and fixed before staining,[1–4] and the other in which a stain is added directly to the centrifuged wet sediment.[5–10] Until recently none of these methods have become popular. The former technics appeared too cumbersome and hence unsuitable for routine laboratory examination. Direct addition of stain to the centrifuged sediment was considered to have no special advantage over ordinary microscopic examination.[11] Interest in the staining of dry smears has been revived by Papanicolaou et al.[12] who proved its merit for the diagnosis of cancers in the urinary tract. In the present report we shall demonstrate that by use of a suitable stain mixture valuable diagnostic information can be obtained by direct staining of the wet sediment.

METHOD

The stain consists of a mixture of gentian violet and safranin in alcoholic solutions as frequently used in the Gram stain. The two stains are made up in our laboratory as follows:

Solution I: Gentian violet
(85 per cent dye content)

Crystal violet	3.0 gm.
95 per cent ethyl alcohol	20.0 cc.
Ammonium oxalate	0.8 gm.
Triple distilled water	80.0 cc.

Solution II: Safranin 0 (95 per cent dye content)

Safranin 0	0.25 gm.
Alcohol 95 per cent	10.0 cc.
Triple distilled water	100.0 cc.

Three parts of the gentian violet solution are mixed with ninety-seven parts of the safranin solution and the resultant mixture is then filtered. This mixture has a pH of 6.0 and stains satisfactorily within a pH range of 4 to 8. Dilution of the stain with buffer solution has little effect on staining characteristics of the elements of the sediment. In highly alkaline urines the stain will precipitate. Fresh stain mixture should be made up every three months, as a fine granular precipitate tends to form on standing.

Only freshly voided urine specimens are used. The sediment is prepared by centrifuging, the overlying fluid is decanted, and a small drop of stain is added to the sediment in the centrifuge tube. The resultant mixture is sharply agitated briefly and a drop is placed on a clean slide and covered with a cover slip. For detailed study the specimens are examined with the oil-immersion lens as well as with the usual magnifications.

GENERAL OBSERVATIONS

White blood cells, epithelial elements and casts take up the stain readily whereas red blood cells stain faintly at most. This difference in staining is of advantage in cases of hematuria in which it is possible not only to differentiate between red and white blood cells at a glance but also to estimate quickly whether the number of white cells corresponds with or exceeds the number expected in ordinary blood. Pyuria in addition to hematuria can therefore be identified with ease. Similarly, the well stained epithelial cells and casts can be recognized readily even in marked hematuria whereas their discovery would be difficult in the unstained sediment.

Leukocytes differ in their staining charac-

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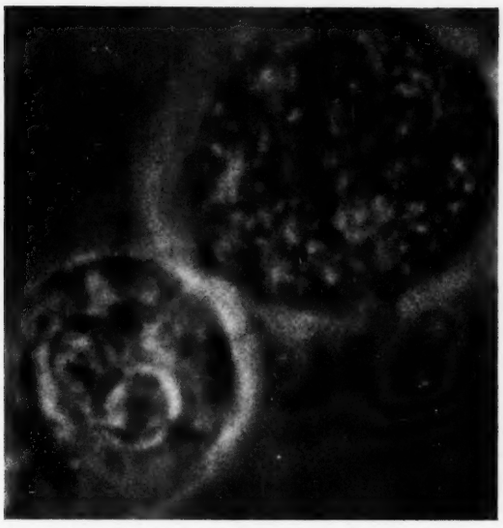

FIG. 1. Normal-sized leukocyte and large white cell with swollen nuclei and motile granules. Phase-microscope photography.

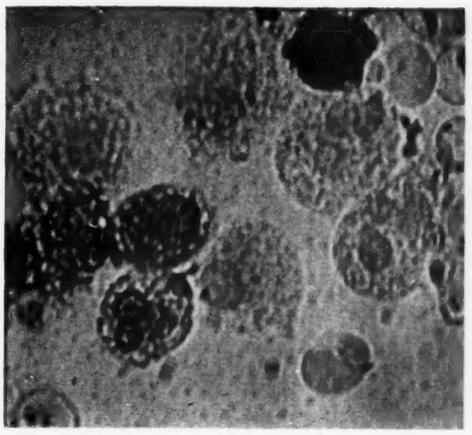

FIG. 2. Deeply stained leukocytes and various forms of large, pale blue-staining cells; oil immersion.

teristics and their morphologic appearance. This variability is diagnostically significant and will be discussed in detail later on. Pus cells stain either deep red to violet or pale blue. The violet-staining cells are of uniform size, contain a dark red or deep purple nucleus and violet granules. They occur commonly in lower urinary tract infections without renal involvement, as in chronic cystitis and chronic prostatitis; they are also found in vaginal pus. The blue-staining cells are either small, of glassy appearance with indistinct nucleus, particularly in urines of high NaCl content; or they appear swollen, much larger than ordinary leukocytes (often twice as large), have a tendency to variability in size or shape, to vacuolization and to extrusion of fragments of cytoplasm. (Fig. 1.) The nucleus in these swollen cells is either multilobulated or seems to be divided into one to four spherical nuclei, generally blue in color; their cytoplasmic granules appear slate gray and, when studied with the oil immersion lens, may show marked Brownian movement. The dancing motion of the granules may vary in intensity. It persists for a long time and may still be observed in urine specimens kept in the icebox for over a week. Small vacuoles may appear among the granules which seem to be pushed back and forth by the granular motion. Sometimes the cell membrane forms a spherical protrusion containing dancing granules which detaches itself from the cell and can be observed as a round transparent ball in which no nuclear structure is visible. If no granules are contained in these transparent globules, they may easily be mistaken for "ghost" cells.

The swollen, pale blue-staining cells with granules showing Brownian movement may be round, oval or pear-shaped. (Fig. 2.) They are identified as leukocytes by a positive peroxidase reaction. Their varying morphologic appearance and their granular movements correspond to changes observed in degenerating leukocytes of the blood[13,14] and of the sputum.[15] The proportion of these cells to the deep-staining leukocytes in urinary sediments may vary considerably. They are present in inflammatory renal diseases, such as acute cystopyelitis, abscess of the kidney and particularly in advanced cases of pyelonephritis in which this type of pus cell predominates. They are absent in normal urines, in essential hypertension not complicated by renal disease, and seem to be rare in glomerulonephritis, at least in its acute and subacute stages.

The cytoplasm of squamous vaginal epithelial cells stains pink to violet, their nucleus deep purple. Bladder epithelial cells appear either colorless or stain a pale blue. Tumor cells appear well stained but from our limited experience it seems that this

stain is less suitable for the recognition of tumor cells than the Papanicolaou stain.

Recognition and identification of the formed elements is greatly facilitated by addition of the stain mixture. Hyaline casts stain a delicate pink to rose shade; granular elements in granular casts stain reddish, violet or bluish in contrast to the unstained, bright and shiny appearing fatty droplets of fatty casts. Inclusion in the casts of cellular elements, red cells, white cells and renal epithelial cells is readily recognized by their several staining characteristics. Fatty cells present a brilliant honeycomb-like structure in a slightly stained matrix.

Bacteria are well stained a dark purple when dead, and either unstained or pink when living and active. Mycelia and spores of fungi appear light and purple.

Trichomonas hominis parasites are either colorless or pale blue. Their motility seems to be impaired by the stain but the vibratory motion of the flagelia is readily appreciated. It is noteworthy that trichomonas infestation of the vagina is associated with the occurrence of swollen, large, pale blue staining pus cells in vaginal pus in the majority of cases.

CLINICAL OBSERVATIONS

The foregoing general description is based on observations, now extending over a four-year period, on ambulatory and hospital patients. The majority of these were hypertensive patients with or without urinary abnormalities and non-hypertensive medical patients with abnormal urinary findings. In the course of our studies a correlation suggested itself between the appearance in the urine of significant numbers of swollen, pale blue-staining pus cells containing motile cytoplasmic granules—"granular motility cells"—and advanced pyelonephritis.[16,17]

This finding seemed worthy of close analysis in view of the difficulties in establishing a clinical diagnosis of chronic pyelonephritis. It is generally agreed that pyelonephritis is often overlooked. Its history and symptomatology are vague; its progress to renal insufficiency is slow and insidious; if associated with marked hypertension its differential diagnosis from other forms of advanced cardiovascular-renal disease, such as the vascular phase of chronic diffuse glomerulonephritis, malignant hypertension or nephrosclerosis, has been notoriously difficult if not impossible. Yet the separation of pyelonephritis from other forms of hypertensive disease is important, particularly for therapeutic reasons.

In order to insure correct interpretation of clinical data only those cases were chosen for analysis in which adequate clinical observations were supplemented with morphologic and histologic examinations at autopsy.

In Table 1 the essential clinical features and autopsy findings of twenty-five patients are reported in whom pyelonephritis was present incidental to congenital malformations, tumor or metabolic disease (Cases 1 to 6); as pyelonephritis *sui generis* (Cases 7 to 10); complicating arteriosclerosis and nephrosclerosis (Cases 11 to 14); presenting the clinical syndrome of malignant hypertension (Cases 15 to 18); resembling chronic glomerulonephritis in history and symptomatology (Cases 19 to 21) and superimposed on acute glomerulonephritis (Case 22). Cases 23 to 25 are representative of the findings in glomerulonephritis.

The cases represent a highly selected group since they were predominantly patients in late stages of renal insufficiency with abnormal urinary findings. In over one-half of the patients impairment of renal function at the time of observation was so pronounced that intravenous pyelography was precluded.

All patients with pyelonephritis showed "granular motility cells" in the urinary sediment. Of the three patients with glomerulonephritis the cells were found in the urine of one (Case 25) who also had suppurative prostatitis. In the majority of cases reported the average urinary specific gravity ranged between 1.006 and 1.012; however, slightly higher specific gravities did not preclude the occurrence of the swollen cells.

They may be found without renal insufficiency (Cases 4, 6 and 10); nevertheless as will be shown, some degree of renal functional abnormality seems to be a factor in their occurrence. In patients 12 and 14, who were followed over several years and presented a picture of essential hypertension, the appearance of cells with granules showing Brownian movement coincided with the findings of cellular casts, a positive urine culture, the development of anemia and deterioration of kidney function.

Large pus cells may originate in the kidney or kidney pelvis. They were found in the cystic fluid of two patients with polycystic kidneys (Cases 2 and 3) and were obtained in the course of retrograde pyelography. In Case 6 in which chronic cystitis and pyelonephritis were present the majority of pus cells in the bladder urine were small and deeply stained, and only a few were of the larger, pale-staining variety; whereas in the urine obtained by catheterization of the left ureter the large cells with Brownian movement of the granules predominated. The swollen cells may, of course, stem from sources further down in the urinary tract. Urinary sediments almost exclusively containing cells with moving granules were frequently observed immediately following prostatic surgery. A typical example is Case 5 in which this finding persisted up to the death of the patient. In patients who recovered from the operation the swollen cells were observed as long as a pale urine of low specific gravity was excreted; with improvement of kidney function in these instances pus cells became small and stained deeply.

Table 1 demonstrates the well known fact that the degree of pyuria gives no indication of the extent of the renal lesion present. Similarly, there is no correlation between the quantity of swollen pus cells in the urine specimens and the degree of pathologic alteration at autopsy. In our experience, however, the appearance in the urine of cells with granules exhibiting Brownian motion invariably denoted a combination of inflammatory process in the urinary tract with renal functional damage, and in those cases that came to autopsy pyelonephritis was found with great regularity. The diagnostic significance of this observation may be illustrated by the following two cases in which the differential diagnosis between pyelonephritis and glomerulonephritis would ordinarily be difficult:

Case 21. W. M., a thirty-five year old white mail order clerk, was admitted to Michael Reese Hospital on May 18, 1946. He had been apparently well until May, 1943, when he contracted mumps from his children and had to leave his work on account of exhaustion. In August of that year he was discharged due to the finding of albuminuria. A few weeks later he applied at another firm and was accepted since no albumin was found on entrance examination. He worked until August, 1944, when he first noticed gradual development of edema of the face, hands, ankles and feet. The edema became worse, and he was confined to bed for one year, kept on a salt-poor diet and ammonium chloride medication. During the last two months of 1945 he was able to work, but in January, 1946, dyspnea, orthopnea and severe nausea developed so that he had to be hospitalized during February and March. A report from that hospital indicated that he had a blood pressure of 180/110, enlarged heart due to hypertrophy and dilatation, albuminuria, hematuria, marked azotemia, acidosis and severe anemia. A diagnosis of chronic glomerulonephritis and hypertensive heart disease was made. Therapy consisted of intravenous fluids and three blood transfusions.

On admission to Michael Reese Hospital the patient appeared well nourished and not acutely ill. There was generalized pallor of the skin and mucous membranes. His temperature was 98.6°F., his pulse rate 72, respirations 18. The blood pressure measured 164/90. The heart was enlarged to the left. The apical impulse was 2 cm. to the left of the mid-clavicular line but was not heaving. The second aortic tone appeared accentuated. The lungs were clear. Liver and spleen were not enlarged. There was no edema. The fundi appeared pale, the discs sharply outlined. The arteries showed no significant alterations in caliber but light reflexes were increased and two flame-shaped hemorrhages were noted in the right eye. The electrocardiogram showed evidence of left heart strain. Blood chemistry, blood count and urinary find-

TABLE 1

CLINICAL AND POSTMORTEM FINDINGS IN TWENTY-TWO CASES OF PYELONEPHRITIS AND THREE CASES OF GLOMERULONEPHRITIS

Case Sex Age	Date of Observations	History	Blood Pressure Range	Serum Levels								Blood Count			Urine*						Retinal* Lesions				Autopsy Findings*					Pathologic Diagnosis
				Urea (mg. %)	Bicarbonate (mEq./L.)	Chloride (mEq./L.)	Calcium (mg. %)	Phosphorus (mg. %)	Albumin (gm. %)	Globulin (gm. %)	Cholesterol (mg. %)	Hemoglobin (gm. %)	Red Blood Cells (millions)	White Blood Cells (thousands)	Albumin	Red Cells	Casts	White Cells	Culture	Motility Cells	Arteriosclerosis	Hemorrhages	Exudates	Papilledema	Pyelonephritis	Arteriolosclerosis	Glomerulonephritis	Kidney Weight	Heart Weight	
1. Male 31	6/5/47 to 8/5/47	Mild hypertension, albuminuria 4 yr.; nephrolithiasis 3 yr.; pallor, weakness, gastric distress	114/64 to 160/100	170 235	8.0 15.8	111 98	6.8 8.1	10.8 10.6	4.7	2.7	222	7.4 13.6	2.3 4.7	8 7	4 4	1 1	0 0	1 1	Alkaligenes faecalis Staphylococcus albus	1 1	0	0	0	0	4	0	0	90	390	Bilateral congenital megaloureter; bilateral renal calculi; chronic, severe bilateral pyelonephritis
2. Male 71	2/6/48 to 2/18/49	Chronic coronary insufficiency 5 yr.; dysuria, flank pain, intermittent fever 3 yr.	135/65 to 180/90	90 180	21 9.8	111 104	8.3 6.9	6.2 8.6	4.2	2.2		12.0 9.7	3.6 3.1	7.4 8.7	2 2	1 1	0 0	4 4	Escherichia coli Esch. coli	4 4	1	0	0	0	4	2	0	450	390	Polycystic kidneys; acute and chronic pyelonephritis; arteriolonephrosclerosis; necrotizing arteriolitis
3. Male 55	8/8/49 to 9/6/49	Weakness, fatigue, cramps in extremities, vomiting, weight loss for few months	130/84 to 144/116	250 119	7.4 19.6	88 87	7.5 7.5	17.0 3.8	4.4 3.4	3.9 3.0	155	8.7 10.0	2.9 3.7	7.7 5.2	1 3	3 4	0 0	4 2	Hemolytic streptococcus Esch. coli	4 2	0	0	0	0	3	2	0	3,550	440	Polycystic kidneys; acute hemorrhagic and suppurative pyelonephritis; hemorrhagic cystitis
4. Female 69	3/3/49 to 3/30/49	Albuminuria, pyuria 5 yr.; dysuria, flank pain 9 mo., constipation, weight loss 6 mo.	130/80 to 170/90	14 19	26.5	107	9.6	3.8			206	11.7	3.9	5.8	3 3	1 0	1	4	Esch. coli	4	2	0	0	0	1	2	0	300	310	Carcinoma of sigmoid colon, linitis plastica type; metastases to right kidney, pelvis of left kidney; chronic pyelonephritis
5. Male 71	6/5/48 to 10/16/48	Diabetes mellitus 15 yr., prostatectomy 6 mo. before; bronchopneumonia	178/94 to 210/84	60 92	24 19	105 99	8.2	4.0	2.4 2.4	4.0 3.5	132	13.4 10.6	4.1 3.5	10.1 14.9	2 4	1 1	1 1	4 4	Staph. aureus Pseudomonas pyocyanea	4 4	1	0	0	0	4	2	0	200	370	Acute bilateral bronchopneumonia; periaortic abscess; chronic pyelonephritis; chronic cystitis cystica
6. Female 70	1/27/47 to 2/17/47	Diabetes mellitus many years; amputation right leg 3 yr. before; chronic cystitis and pyelonephritis since	150/80 to 240/100	20	28	100	8.4	3.3	3.5	3.0	347	11.1	3.7	18.4		4	0	3	Aerobacter aerogenes	1	2	1	0	0	1	4	0		650	Arteriosclerosis and arteriolosclerosis of kidney; focal pyelonephritis; chronic cystitis; ruptured aneurysm of abdominal aorta; perirenal hematoma
7. Female 16	4/12/46 to 6/9/46	Fatigue, pallor few months; upper respiratory infection 2 wk.; edema of face, ankles, anasarca few days	120/75 to 170/110	35 240	10 12	98 80	7.8 10.9	7.0 10	3.2 4.5	2.9 1.6	163	5.2 8.5	1.9 3.2	8.5 5.5	4 4	4 3	0 0	4 4	Esch. coli Staph. albus.	4 4	2	1	1	0	4	2	0	R 45 L 25	200	Acute pyelonephritis superimposed on pyelonephritic contracted kidney; chronic cystitis; generalized anasarca, bilateral hydrothorax
8. Female 16	11/11/49 to 12/21/49	Weakness, pallor 2 yr.; cramps in extremities, pedal edema 1 yr; convulsions 10 mo. ago; furuncles 2 mo. hypertensive encephalopathy	150/70 to 210/130	211 161	8.1 25	88 101	5.1 8.8	11.8 6.6	4.0	2.7		5.1 10.5	1.65 3.5	28.1 8	4 4	1 3	0 0	1 1	Esch. coli	1 1	0	0	0	1	4	1	0	100	330	Chronic pyelonephritis with moderate arteriosclerosis; arteriolar necrosis kidneys and brain; interstitial pneumonitis
9. Male 47	7/15/46 to 7/13/47	Hypertension, albuminuria 30 yr.; dyspnea, polydipsia, polyuria several years; furunculosis	195/98 to 205/115	40 175	21 15	98 102	11.4 5.5	5.1 5.0	4.8 4.2	2.4 2.0	232 156	10.0 15.0	3.2 4.7	7.9 13.5	2 4	1 1	0 0	3 3	Staph. albus	3 3	1	0	0	0	3	1	0	225	600	Acute pyelonephritis; chronic pyelonephritis; acute cystitis; healed and recent myocardial infarcts
10. Male 16	9/17/48 to 3/9/49	Acute anterior poliomyelitis with bulbar involvement; in respirator during entire illness	170/95 to 252/140	21 58	32 32	99 88	13.1 14.6	4.0 5.4	3.1	3.9	134	17.6 12.4	5.4 4.1	10.8 12.1	1 2	0 1	1 2	1 2	Staph. albus	1 1	1	0	0	0	2	1	0	340	280	Acute anterior poliomyelitis; marked subacute pyelonephritis; calcific deposits in tubules
11. Male 19	12/7/46 to 12/18/48	Splenectomy 1940, blood pressure then 116/50; hypertension, asymptomatic, discovered 9/1946; sympathectomy May and June 1947	184/110 to 225/150	14 225	25 19	99 90	8.5 10.3	3.3 8.0	5.4 2.0	2.3 3.2	163	15.6 8.2	4.7 2.6	10.7 17.0	3 3	1 3	2 2	0 2	Streptococcus faecalis Staph. albus	0 2	0	0	0	0	4	2	0	180	400	Chronic pyelonephritis; acute pyelonephritis; acute necrotizing arteriolitis of both kidneys; bronchopneumonia
12. Male 46	8/8/47 to 9/19/47	Fatigue, weight loss 3 mo.; hematuria 1 mo. ago for 10 da.; vomiting; few weeks	230/150	34 100	21 23	78 89	9 8.7	5.2	4.2	2.1		15.0 15.0	4.9 4.7	14.2 12.0	4 4	2 4	2 2	2 2	Streptococcus viridans Alk. faecalis	1 1	4	2	3	4	1	4	0	350	525	Generalized arterio- and arteriolosclerosis; nephrosclerosis, pyelonephritis and arteriolonecrosis

13. Female 38	3/23/48 to 5/8/48	Hypertension, headaches 16 yr.; dyspnea, nocturia, ankle edema 6 mo. blood pressure in 1946 150/110, in 1947 196/130; sympathectomy right side 4/28/48	230/170 to 200/110	30 200	33 29	98 102			4.8	2.7		13.3	3.6	10.0	4	1	1	2	Staph. albus	1	1	0	0	0												**Chronic pyelonephritis with arteriosclerosis; right retropleural hematoma; massive collapse of right lung**
												9.3	2.8	14.9	4	1	1	2	Esch. coli	1	2	2	2	2	2	2	0	175	275			
14. Female 57	5/15/48 to 5/29/49	Hypertension, asymptomatic, 11 yr.; observed since 1942, blood pressure then 235/135	210/115 to 290/150	65 254	24 6.2	102 93	9.5 8.1	1.8 15.4	4.4 4.1	2.3 3.7		11.5 11.3	4.2 3.2	6.0 7.8	4	2 1	2 2	3 2	Anhemolytic streptococcus	1	4	2	2	0												**Chronic pyelonephritis; acute pyelonephritis; arterio- and arteriolosclerosis; fibrinous pericarditis**
																				1	4	2	2	0	3	3	0	160	750			
15. Female 26	4/24/49 to 6/11/49	Upper respiratory infection 2 wk. before; blurring of vision; vomiting 4 da.; severe headaches 2 da.	250/110 to 240/150	23 190	28 16	89 94	9.9 9.8	5.2 11.1	3.8 2.3	3.8 2.9	358	12.4 8.7	4.5 3.1	10.4 20.0	2 4	4 1	0 0	1 3	Esch. coli Anhemolytic streptococcus	2	2	2	4	4	3	2	0	R 55 L 225	520			**Acute pyelonephritis, bilateral, superimposed on chronic pyelonephritis; right contracted kidney; generalized edema; hydrothorax**
16. Female 17	1/27/48 to 1/29/48	2 induced abortions 6 and 9 months before; sore throat, oliguria 2 wk.; abdominal cramps, edema 3 da.	190/128	240	10.4	90	7.2	16.0				15.0	5.3	15.3	4	3	0	2		2	1	2	3	4	4		0					**Only histologic sections available; severe acute and chronic pyelonephritis**
17. Male 27	9/8/47 to 9/19/47	Kidney disease with generalized edema 1942; headaches, blurring of vision, sore throat 10 da. ago	220/150	106 115	15 25	104 94	8.4	7.1	3.9	2.3		11.9	3.8	6.0	4	2	2	2		2	2	4	4	3	3	2	0	250	480			**Chronic pyelonephritis with superimposed arteriolonecrosis**
18. Male 43	10/31/47 to 11/14/47	Known hypertension 1 yr.; intermittent hematuria 7 mo.	180/110 to 220/160	370 290	22 23	72 75	7.3 7.1	9.8 8.8	3.6 3.9	3.5 3.5	163	8.7 11.4	2.9 3.5	10.7 12.5	4 4	3 2	1 1	4 4	Hemolytic staphylococcus aureus	4 4	3	4	4	4	3	3	0	200	575			**Chronic pyelonephritis and arteriolonephrosclerosis with arteriolonecrosis; purulent cystitis**
19. Male 43	9/15/48 to 10/16/48	Kidney disease with hematuria 1928; albuminuria and intermittent hematuria since; progressive weakness, blurring of vision, headaches 2 mo.	170/100 to 238/130	160 217	16 18	99 88	6.7 9.5	12.0 15.5	3.1 3.0	3.5 3.1	224	11.4 8.0	3.8 2.5	10.2 6.3	4 4	3 2	1 1	4 4	Hemolytic staphylococcus aureus Anhemolytic strep.	4 4	2	3	3	2	4	3	0	375	445			**Chronic pyelonephritis with terminal arteriolonecrosis; old healed endocarditis, mitral valve**
20. Male 28	9/14/49 to 10/8/49	Albuminuria since age of 15; in 1942, blood pressure 160/90; headaches, blurring of vision several weeks	200/130 to 290/135	176 330	20 17	84 72	5.8 7.1	13.0	3.5 4.3	2.6 2.6		7.8 7.5	2.5 2.3	6.8 8.7	4 2	3 3	1 1	1 1		1 1	3	4	3	3	4	3	0	240	550			**Acute pyelonephritis superimposed on chronic pyelonephritis, with necrotizing arteriolitis of kidneys and large intestines**
21. Male 37	5/18/46 to 3/19/48	Albuminuria following mumps 1943; generalized edema 1944; dyspnea, pallor, insomnia, headaches, nocturia since 1946	154/84 to 240/135	53 290	18 11	111 90	9.1 8.9	6 16	4.3 3.6	1.2 1.6	200 153	5.5 9.1	2.0 2.8	6.4 10.0	4 4	3 3	1 2	4 4	Staph. albus	4 4	1	1 3	0 2	0 0	4	3	0	250	575			**Chronic pyelonephritis; arteriolonephrosclerosis; bronchopneumonia, terminal**
22. Male 13	10/11/47 to 11/2/47	Epigastric pain, generalized edema, vomiting 1 wk.; hematuria 2 da.; convulsions, hypertensive encephalopathy	140/98 to 190/140	100 240	15 27	92	6.3		3.2 3.2	1.9 2.2	126	9.0 8.0	3.6 2.8	8.9	4	2 4	2 2	2 4	A. aerogenes	4	0	0	0	0	3	0	3	175	175			**Acute pyelonephritis superimposed on subchronic glomerulonephritis; acute serous myocarditis**
23. Male 17	5/18/46 to 4/24/48	Generalized edema, polyuria, albuminuria, microscopic hematuria 9 mo., in hospital marked edema, terminal convulsions	180/90 to 210/140	11.7 200	28 18	100 84	9.4 4.7	4.8 17.0	2.4 3.6	2.1 1.5	313 160	14.0 12.0	4.5 3.6	8.6 23.2	4 4	3 1	3 2	3 3	Str. viridans	0 0	0	0	0	0	0	0	4	200	450			**Subchronic glomerulonephritis; organizing fibrinous pericarditis; hematopericardium**
24. Female 21	11/20/47 to 11/23/47	Thrombophlebitis after appendectomy 6 yr. ago; rheumatoid arthritis 10 mo. ago, blood pressure then 140/100; nausea, vomiting, diarrhea 3 mo. ago; hematuria, edema 1 mo.	140/100 to 240/115	135	20	95	7.5	15.2	1.9	2.5	145	7.5	2.6	10.6	4	3	3	3	Str. viridans	0	0	1	3	2	0	0	4	390	400			**Subacute glomerulonephritis, arteriolonecrosis with multiple infarctions of glomeruli; acute endocarditis superimposed on old healed endocarditis; acute myocarditis**
25. Male 54	6/22/49 to 7/3/49	Bilateral caseopneumonic tuberculosis 1948; right thoracoplasty February 1949; epigastric distress 2 mo., generalized twitching, stupor 2 da.	130/80 to 184/98	109 108	20 22	86 83	9.7 8.1	6.4	3.2	3.2	152	8.2 8.2	3.4 3.2	22.1 16.4	4 4	4 4	1 1	2 2	Str. viridans Staph. albus	2	0	0	0	0	0	0	4	400	440			**Subacute glomerulonephritis; acute arteriolonecrosis; miliary tubercles in the kidneys; acute suppurative prostatitis**

*Graded 0 to 4.

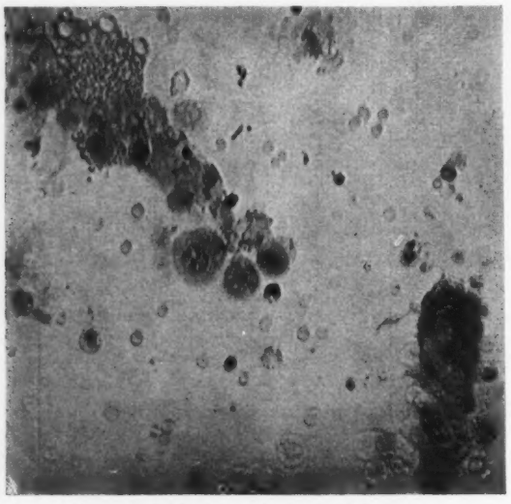

FIG. 3. Stained sediment of Case 21.

ings are given in Table I. Urea clearance was 14 per cent of average normal function. A phenolsulfonpthalein test showed 2½ per cent dye excretion in the first hour, the same amount in the second hour. In a dilution test after ingestion of 1,500 cc. of water, only 840 cc. were excreted within four hours; the highest half hour volume was 160 cc. Nevertheless, the specific gravity fell to 1.001. On a concentration test a specific gravity of 1.012 was reached. The stained sediment was characterized by numerous hyaline, granular and cellular casts, some of which contained small fatty droplets; 40 to 60 red blood cells and 20 to 40 white blood cells per high power field; many renal epithelial cells and fat droplets, found inside and outside the epithelial elements. Among the pus cells "granular motility cells" predominated. (Fig. 3.) The urine culture was negative.

The patient was given blood transfusions and discharged after eighteen days of hospitalization. After resting all summer he started to work part-time in January, 1947. During 1947 he was followed at the Renal Clinic and was readmitted to the hospital four times for short periods to receive blood transfusions. His blood pressure throughout this year was about 185/110, the hemorrhages in the fundi disappeared and no new retinopathy was noted during that time. His cardiovascular status remained stationary. Albuminuria and sediment findings continued unchanged. The average specific gravity of the urine varied from 1.008 to 1.014 (not corrected for albumin), and the urinary output ranged from 1,800 to 2,700 cc. daily. Azotemia and acidosis gradually increased. Hypoproteinemia and anemia continued in spite of repeated blood transfusions. Throughout the year the urine culture remained negative and body temperature was normal at all times.

From December, 1947, on signs of cardiac failure became prominent and the patient had to be hospitalized almost continuously. Dyspnea, orthopnea and edema of the pelvic region, the scrotum and the lower extremities developed. The blood pressure rose to 220/112. After temporary improvement on a rice diet, symptoms of hypertensive encephalopathy appeared. Headaches, blurring of vision, dizziness and staggering gait were noted. Hemorrhages and cotton-wool exudates were now present in the eyegrounds. At times the blood pressure was as high as 240/135. A urine culture, taken in February, 1948, was positive for Staphylococcus albus. The patient died in March, 1948.

The clinical diagnosis was chronic glomerulonephritis, late stage, but in December, 1947, a tentative diagnosis of pyelonephritis superimposed on chronic glomerulonephritis was made. The autopsy, however, revealed macroscopic and microscopic evidence of only chronic pyelonephritis and arteriolosclerosis.

Differential diagnosis was difficult in this patient because he was first observed in a late stage of renal disease, showed fatty elements in the urine, had hypoproteinemia and a negative urine culture during the larger part of his illness. Prior to December, 1947, we did not feel justified in attributing too much diagnostic significance to the predominance in the sediment of the cells with granules exhibiting Brownian motion.

CASE 22. R. A., a thirteen year old colored male, was admitted on October 11, 1947, to the Pediatric Service with a history of epigastric pain, vomiting, generalized edema for one week and hematuria of one day's duration. Except for dysentery at five months of age associated with convulsions, and scarlet fever followed with an otitis media at the age of five years, the boy appeared to have been well up to the onset of the present illness. On admission the temperature was 98.4°F., pulse rate 84, respirations 26. The face appeared edematous, the abdomen was distended by fluid and flank dullness was present. There was little edema of the extremities. The heart was slightly enlarged. A soft systolic murmur was present over the apex and transmitted to the axilla. The blood pressure measured 140/98. The eyegrounds showed no abnormali-

ties. The urine contained 4 plus albumin, had a specific gravity of 1.010; the unstained sediment revealed many red blood cells, 20 to 25 white blood cells per high power field, 8 to 10 granular, 2 to 3 waxy and 3 to 4 hyaline casts. The blood findings are given in Table 1.

On the second hospital day the child had convulsions, became lethargic, stuporous, and the blood pressure rose to 190/140. He was given magnesium sulfate intravenously and sedated. After temporary improvement, during which the child's mental condition cleared, he became increasingly edematous, developed progressive oliguria, azotemia and acidosis. On October 27th he was seen by us in consultation. At this time the sediment showed 20 to 30 red blood cells, 2 to 3 granular casts and 30 to 40 white blood cells per high power field. All the white blood cells were of the large, pale-staining variety with granules showing Brownian movement. A tentative clinical diagnosis of acute pyelonephritis superimposed on existing glomerulonephritis was entertained. A subsequent urine culture revealed Aerobacter aerogenes. The child expired on November 2, 1947. At autopsy acute pyelonephritis superimposed on a subchronic glomerulonephritis was found.

In contrast to the microscopic urinary findings in these patients the urinary sediments in patient 23, who had a consistent history of subchronic glomerulonephritis, did not contain granular motility cells during a two-year observation period, except on two occasions when an occasional cell was found after prolonged search. This was true despite the presence in the urine culture of Streptococcus viridans.

We may add that although the number of our clinical observations in acute glomerulonephritis is small, we have not been able to find large cells with granules showing Brownian movement in any instance.

SIGNIFICANCE OF THE VARIETY OF PUS CELLS

The demonstrated correlation between the finding in the urinary sediment of pale blue-staining, swollen white cells exhibiting Brownian motion of their cytoplasmic granules and the presence of pyelonephritis raises the question as to the factors involved in the production of this phenomenon. Theoretically, variations in the morphologic appearance of leukocytes that have passed into the urine may be due to (1) a change in the osmotic properties of the surrounding fluid, i.e., urine versus blood; (2) the effect of chemical or bacterial agents in the urine; (3) alterations of the physico-chemical structure of the leukocyte before passing into the urine and (4) differences in the osmotic resistance of the various types of leukocytes.

In order to investigate the influence of the composition of the urine on staining and morphologic appearance of the leukocytes, a number of simple experiments were performed.

Oversized, blue-staining pus cells, exhibiting variability in size and Brownian movement of granules, were transferred from pyelonephritic urines into normal urines, thoroughly mixed with these urines and centrifuged. On re-examination these cells appeared small, shrunken, uniform in size, of glassy appearance with indistinct nuclei and completely immobile granules. Their staining properties remained unaltered. This process proved to be reversible; retransferred into the pathologic urines, these same cells assumed their original form and exhibited Brownian motion of the cytoplasmic granules.

A similar phenomenon was observed with leukocytes of normal blood. After removing the sediment from a pyelonephritic urine a drop of normal blood was suspended in this urine, then centrifuged and stained. On microscopic examination most of the polymorphonuclear leukocytes of the added blood appeared swollen, stained pale blue, and their granules exhibited agitated motion. When suspended in normal urine the leukocytes of normal blood were small, uniform in size, pale blue and contained immobile granules.

Transfer of swollen pyelonephritic pus cells into physiologic saline solution produced the same reversible changes as transfer into normal urines. In contrast to

this transfer into isotonic urea solution led to irreversible changes. The cells shrank, cytoplasm and nucleus took on a deep violet staining, and a tendency to clumping of the cells developed.

Transfer of the swollen cells of a pyelonephritic urine into distilled water or into the extremely hypotonic urine from a patient with diabetes insipidus resulted in rupture of the cells and a deep violet staining of protoplasm and nuclei.

From these observations, it is safe to conclude that urinary pus cells, like leukocytes in other body fluids, are subject to changes in size and appearance by alterations in the suspending solution. The blood leukocyte or urinary pus cell, therefore, appears to act as a biologic indicator of the composition of the urine. This finding is in contrast to the current disregard of the variations in morphologic appearance of urinary pus cells, variations which are generally considered to be only a hindrance to proper differentiation of pus cells from renal tubule cells.[18,19] A review of the pertinent data in the literature, however, will show that the significance attributed by us to the variability of pus cells is supported by a large number of experimental and clinical observations. Thus differences in the wet staining of urinary pus cells were described as early as 1884.[20] Later by use of sodium alizarinsulfonate a correlation was noted between staining characteristics of pus cells and clinical conditions. Pus cells in cases of acute urinary tract infections remained unstained but stained deeply after the acute symptoms had subsided.[21–23] Similar observations with a congo red-trypan blue stain mixture led to the assumption that the non-staining pus cells represented "living" hence fresh white cells, whereas the deep-staining cells were old and dead.[7,24] This was not confirmed since urinary pus cells may fail to stain even after two or three days when they are certainly dead,[25] which is in accord with our own observations. The factors responsible for the variability in staining are complex and in part identical with those producing morphologic changes. Hence, they will be discussed together.

The morphologic changes, namely, nuclear variability, changes in cell size, vacuolization, extrusion of fragments of protoplasm, and particularly Brownian motion of granules, which are so commonly observed in urinary pus cells of advanced cases of pyelonephritis have received little attention in the literature. The various forms of urinary pus cells were described in the last century,[20] but no correlation with clinical conditions was made until in 1908 the occurrence of Brownian movement of granules in these cells was noted.[26] Shortly afterward it was pointed out in a discussion that "from the point of view of differential diagnosis, the presence of numerous glittering leukocytes in the urine speaks for pyelonephritis or kidney abscess and against cystitis."[27] It seems that no further elaboration of this statement appeared and that it has since remained forgotten.

The changes in form and size of urinary leukocytes are due in part to osmotic effects. The morphologic integrity of polymorphonuclear leukocytes is maintained optimally in isotonic or slightly hypertonic solutions.[28,31] Activity of pseudopods is also conserved best within this range.[29] A progressive increase above[30] or below this level[31] have been found increasingly destructive for leukocytes.

Variations in the osmotic pressure of the suspending fluid will lead to inversely proportional volume changes of leukocytes. Pus cells, when placed in hypertonic or hypotonic Ringer-Locke solutions respectively, will decrease or increase in size. These volume changes are completely reversible. Equilibrium volume is reached about thirty minutes after placing the cells into the solution.[32]

The changes in the morphology of leukocytes or pus cells when placed in hypotonic solutions are of particular interest in view of the similarity with the pus cell changes in pyelonephritic urines. The cells enlarge, become spherical, the nuclei partake in the swelling and Brownian movement of gran-

ules appears until the cell approaches equilibrium volume. In very hypotonic solutions a bleb of cytoplasm is exuded at some point of the cell surface, and shortly afterward the white cell contents explode, leaving behind the nucleus and débris.[32,33] The occurrence of Brownian movement of granules depends on the electrolyte concentration of the suspending solution and has been studied quantitatively. In blood leukocytes granular motion can be induced by immersion in hypotonic NaCl solutions between 0.2 and 0.4 per cent whereas above and below these concentrations the granular movements will cease.[34,35]

It would appear reasonable, then, to infer that the observed occurrence of swollen pus cells with granules exhibiting Brownian movement in pyelonephritic urines could be due to hypotonicity. This concept would find support in the clinical experience that there is a characteristic tendency to excretion of persistently hypotonic urine for many years in patients with pyelonephritis.[36,37] Their capacity to concentrate electrolytes in the urine is impaired early in the disease.[38] In the later stages diluting ability is frequently maintained almost to the end,[39,41] in contrast to the later stages of malignant hypertension and chronic glomerulonephritis in which the production of a more isotonic urine is a characteristic feature.[40]

Yet the phenomena are more complex. Urines of identical low specific gravities (and comparable pH and titratable acidity) may show a difference in staining, size and granular motility of pus cells. Brownian movement may also be found in solutions with specific gravities up to 1.018, certainly hypertonic. Osmotic factors, therefore, seem only partially responsible for the observed variability of pus cells.

In a composite solution like urine, a variable number of direct chemical effects on pus cells might be anticipated. Urea in sufficient concentration, for instance, will produce pronounced alterations of both protoplasm and nucleus of leukocytes. Isotonic solutions of urea destroy leukocytes within six hours, whereas isotonic NaCl solutions preserve the cells.[42] By replacing NaCl with an isotonic proportion of urea solution an increasing number of pus cells will be damaged.[42] In a pyelonephritic urine the large, pale blue cells will shrink, stain deep red or purple, and their granular motion ceases when the urine is mixed with isotonic urea solution, thus simultaneously lowering the NaCl content and increasing the urea content of the urine. Other known direct chemical effects on pus cells which are of importance in urine are the protective effect of colloids,[31] particularly proteins,[35] and the damaging action of dilute ammonia which induces Brownian movement of granules in isotonic solutions.[35] Of special interest also is the calcium content of the urine. Lowering of the calcium content of the urine below a critical level of 6 mg. per cent has been shown to be responsible for differences in staining of urinary pus cells with sodium alizarinsulfonate, a finding which has been made the basis for differentiation of cystitic and pyelonephritic pyuria.[44] In renal functional impairment urinary calcium excretion is decreased.[45,46] We have found quite frequently that no precipitation of calcium occurs on addition of Sulkowitch reagent to urines with swollen, pale blue-staining pus cells; whereas in urines of the same specific gravity with positive Sulkowitch reaction the pus cells were of the small deep-staining variety. There are, however, exceptions. Finally, bacteria and their products have been found to produce functional and morphologic changes of pus cells *in vitro*[47,48] involving reduction of phagocytic processes, loss of ameboid movement and marked swelling of leukocytes. The effect of these agents on pus cells in pyelonephritic urines has not been studied as yet.

The variable composition of the final urine, however, cannot be the only factor in determining the morphology and staining of pus cells since a single urine specimen may contain pus cells of varying form and

staining. Several other influences may play a role. Pus cells entering the urine from the blood stream by way of the nephron are subjected to varying osmotic pressures and varying concentrations of urea and NaCl during the process of urine formation. Hence their form and appearance may differ from that of pus cells originating from the lower urinary tract which are affected only by the final urine.

Another possible factor is that the leukocytes of the blood have undergone physicochemical alterations before passing into the urine. It has been shown that osmotic resistance may vary for different leukocytes of the same blood. It is rather uniformly high in normal blood but differs widely in intoxications and infectious diseases so that a variable number of leukocytes will respond with alterations of size and viscosity to the same hypotonic concentrations.[49] There exists also a difference in the osmotic resistance of the various types of leukocytes. Lymphocytes, in contrast to polymorphonuclear leukocytes, retain their morphologic integrity longest in hypotonic solutions and eosinophiles seem little affected either by hypotonic or hypertonic solutions.[28] These data are of importance in view of the fact that in acute and subacute glomerulonephritis lymphocytes predominate in urinary pus cells whereas in pyelonephritis the large majority of pus cells are polymorphonuclear.[2,50]

From the evidence available it would appear that both the variable osmotic resistance of leukocytes and the composition of the urine are responsible for the variability in form and staining of urinary pus cells. Much investigation remains to be done and the information on hand is admittedly incomplete.

SUMMARY

A new stain for urinary sediments is described which permits easy recognition of the cellular and formed elements. Among the urinary leukocytes larger, pale blue-staining cells can be observed which are characterized by their tendency to variability in size and shape, to vacuolization, extrusion of fragments of cytoplasm and to Brownian movement of their cytoplasmic granules.

A correlation was found between the occurrence of these cells in the urine and the presence of pyelonephritis, as established by clinical observation and postmortem findings in twenty-five cases.

That the composition of the urine influences the form and staining properties of the urinary leukocytes was demonstrated by laboratory experiments.

The various factors likely to produce morphologic and structural alterations of pus cells in pathologic urines are discussed.

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Aspiration Biopsy of the Kidney*

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ASPIRATION biopsy of tumor tissue is a classical procedure for examination of the nature of neoplastic disease but this method has not been applied extensively to diseases of the parenchymatous organs, in which only liver and spleen biopsy has been employed to any great extent. The liver biopsy technic as described by Iversen and Roholm in 1939[1] has proved to be a useful aid in the differential diagnosis between obstructive jaundice and parenchymatous jaundice. Moreover, this technic has increased our knowledge of the histopathology of the liver both in acute and chronic hepatic disorders.

Apparently no attempt has thus far been made to perform investigations of renal tissue by aspiration biopsy. The literature on the subject contains reports only on the results of biopsies of kidneys obtained in the course of surgical treatment of hypertension[2,3] but no investigations in intrinsic renal disorders have been published. Therefore we have attempted aspiration biopsy of renal tissue in the hope that additional information about the histopathology of the kidney could be obtained in this way. In the following pages an account will be given of the results obtained so far.

Even if microscopic examination does not afford complete information about the functional state of an organ, there can hardly be any doubt that comparison of the results of functional tests and the corresponding histologic picture constitutes one of the best means of becoming acquainted with the pathologic processes and their influence on the function of the organ. Consequently, we have made comprehensive renal function tests in connection with biopsy of the kidney.

The conditions in which the renal biopsy technics will presumably be of greatest value are those mild renal disorders which only rarely come to autopsy and also the initial stages of the severe, acute renal disorders. A group of diseases especially useful to examine in greater detail by means of biopsy is that of the acute anurias occurring after shock, uteroplacental damage, poisoning with sulfonamides or corrosive sublimate, enteritis, and from many other causes. At present it is common usage to classify all these conditions under the term "lower nephron nephrosis"; but it is doubtful whether such generalization is permissible, and a closer investigation of the histological changes in milder, non-fatal cases of this nature is much needed.

The histologic picture obtained by postmortem technics generally used is frequently affected by autolysis, permitting an estimate of only the coarsest vascular, connective tissue and inflammatory changes. Like other cells with marked metabolic activity the tubular cells of the kidney are subject to great agonal and postmortem changes. These are not of the nature of actual putrefaction but are presumably metabolic processes which continue after death and follow a more or less abnormal course, thus changing the structure of the cells. In the case of biopsy of the kidney, fixed in a suitable manner, the histologic picture will, on the other hand, show the structure of the kidney as it was *in vivo*.

TECHNIC

Biopsy of the Kidney. The instruments used for this purpose were the same as were described by Iversen and Roholm for liver biopsy: (1) syringe, needle, and a 2 per cent procaine solution for local anesthesia; (2) a lancet; (3) a needle measuring 180 mm. in length, the external diameter being 1.9 mm., with a pointed stylet and a very sharp, slightly serrated edge; (4) a 20 ml. tight-fitting syringe the piston of which can be fixed in all positions by means of a special fixation device.

Before the biopsy is obtained, intravenous (if desired, direct) pyelography is performed with a lead mark on the skin approximately over the site of the *right* kidney. By means of exposures in

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two planes with the patient in the sitting position the site of the kidney and its distance from the lead mark are determined, after which the site of the puncture is marked off. With the patient in the same position the skin is disinfected and under local anesthesia a small incision is made in order to facilitate introduction of the needle. The needle is introduced nearly up to the surface of the kidney, according to the distance measured in the x-ray; the stylet is removed, syringe and needle are assembled and the piston is pulled back and secured by means of the fixation device. The needle is pushed in by screwing it another 3 or 4 cm. into the tissue, and then needle and syringe, in which the vacuum is retained, are pulled out. The barrel of the syringe will, as a rule, contain a cylinder of renal tissue measuring from 10 to 20 mm. in length. The specimen is fixed *immediately* on a small piece of cardboard in 93 per cent alcohol (per cent by weight) which, because of the thinness of the tissue, will complete the fixation in a very short time. It is important that the tissue not be allowed to dry up in the course of these manipulations.

Renal Function. Immediately after the biopsy of the kidney we have made renal function studies which, in addition to the urea and creatinine clearances comprise, among other things, the inulin clearance as a measure of the glomerular filtration rate, para-amino hippuric acid clearance as a measure of the effective renal blood-flow, and Tm_{PAH} expressing the tubular excretory mass for p-amino hippuric acid; also, Addis's concentration test. The technic employed for the renal function tests will not be dealt with in detail here but reference may be made to previous publications on this subject.[4–6]

Risks in Biopsy of the Kidney. At the time of this writing eighty biopsy attempts have been made in sixty-six patients. Sufficient kidney tissue to permit histologic examination was obtained in only forty-two cases. Most of the failures were encountered in the beginning. With greater experience we now get a positive result in at least two-thirds of the cases. Complications other than transient hematuria have not occurred in any of the cases. In most cases the hematuria has been of only six to twelve hours' duration, and sometimes it can be ascertained only by means of microscopic examination. In one case a small clot was passed.

Postmortem examination sooner or later after the biopsy could be made in ten cases. In three of these cases a small hematoma, corresponding to 5 to 10 ml. of blood, could be demonstrated in the perirenal fatty tissue but in most cases no trace of the biopsy could be demonstrated. Injury to the renal tissue was not found in any of the cases.

Because of the location of the large vessels and of the spleen the biopsy was made from the *right* kidney in all cases but one. Biopsy was not made in patients with hemorrhagic diathesis or with severe obstruction to the urinary flow from the kidney to be examined.

RESULTS

The following is a report of the preliminary results of biopsy examinations in six patients suffering from various renal disorders. As our knowledge of the histologic changes in preparations of this nature is still slight, only the most brief description of our findings will be given.

The histologic picture differs in several respects from that usually found in microscopic examination of kidneys obtained at autopsy, and, therefore, the results of two biopsies from patients with normal renal function will be given first. (Figs. 1 and 2.)

The biopsy material obtained by means of this technic differs from the usual postmortem material chiefly in the following respects: (1) The tubules, in particular the proximal and distal convoluted tubules, have a large lumen; they convey the impression of being "dilated" especially when the diuresis is low. (Fig. 1.) With increasing diuresis the lumina of the proximal tubules are narrowed. (2) The delimitation of the cells toward the lumen in the proximal convoluted tubules is very poor. In many cases there seem to be remnants of protoplasm in the tubule, and no actual limit can be drawn between cell and lumen. (Fig. 2.) (3) The capillary coils of the glomeruli convey the impression of being gaping; most frequently they contain no blood. (4) Precipitates, resembling protein, may be found in the capsular spaces even in cases in which no proteinuria is found.

Case 1. A thirty-nine year old woman, previously in good health, after a febrile abortion developed moderate jaundice and severe anuria. The period of oliguria lasted about two weeks during which the serum urea rose to 505 mg. per cent. On the eighth day of the disease biopsy of the right kidney was made. The output of urine was 70 ml. during these twenty-four hours.

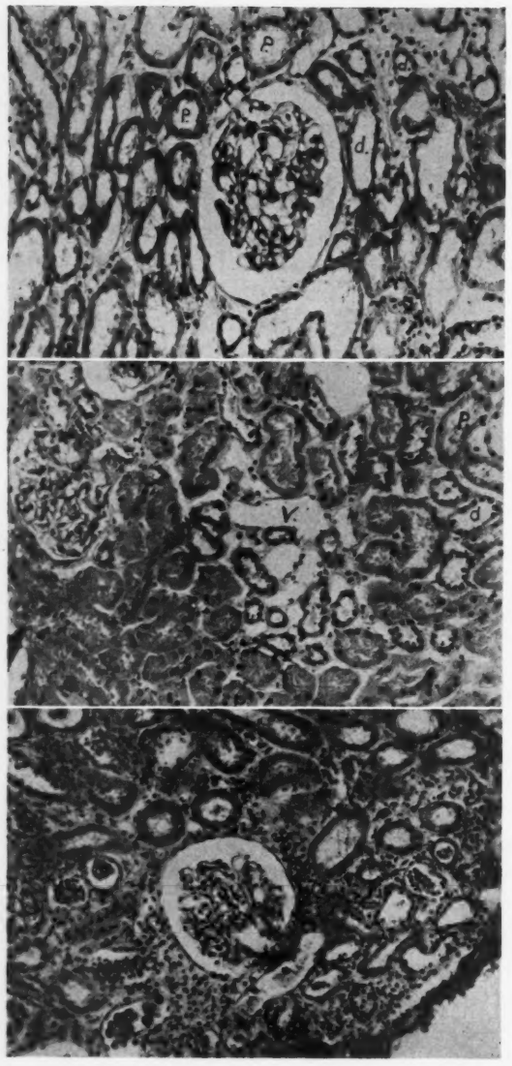

FIG. 1. Normally functioning kidney; note large lumens of proximal (*p*) and distal (*d*) convoluted tubules. The capillary loops of the glomeruli seem to contain no blood. × 180.

FIG. 2. Normally functioning kidney; note tall cells in proximal convoluted tubules with ill defined delimitation toward the luminal border. The cells of the distal convoluted tubes are lower and more nuclei are seen in each section. In the center is a thin-walled vein (*v*); × 180.

FIG. 3. Tubular nephritis following febrile abortion (eighth day); heme casts, containing lymphocytes, leukocytes and remnants of nuclei in distal convoluted tubules and loops of Henle. Interstitial cell infiltration (lymphocytes, histiocytes and a few plasma cells); the glomeruli contain no blood in the loops; proximal convoluted tubules with low epithelium and wide lumina contain remnants of protoplasma; × 140.

The patient was treated with parenteral feeding with a 50 per cent glucose solution, correction of the electrolyte equilibrium, blood transfusion, antibiotics, etc., and was discharged in good health two months later.

Figure 3 shows the histologic picture. The glomeruli appear to contain no blood in the coils but are apparently normal otherwise. The proximal convoluted tubules show a low epithelium and a wide lumen but do not differ distinctly from the normal. In Henle's loops and in particular in the distal convoluted tubules numerous heme casts are seen, often containing lymphocytes, leukocytes and remnants of nuclei. The epithelium is well retained everywhere; however, in the tubules containing casts it is often flattened. There is no necrosis of the tubular cells anywhere.

In the interstitial tissue there is slight edema and in several areas a marked cell infiltration, chiefly lymphocytes and histiocytes but very few plasma cells. The interstitial cell infiltration seems to be without any relation to the occurrence of casts. *Histologic diagnosis:* tubular nephritis.

Table 1 shows the results of renal function tests made on the thirteenth, nineteenth, thirty-second and sixty-second days, respectively, after the onset of anuria. To begin with, all the renal function tests showed much reduced values but the glomerular filtration rate (inulin clearance) was comparatively less impaired than the tubular secretion (Tm_{PAH}) so that the ratio I/Tm (glomerular filtration rate:tubular excretory mass) is much increased at the beginning, and falls only slowly toward normal. Two months after the episode of anuria the filtration rate was about 50 per cent, the tubular secretion 33 per cent of normal.

Comment. Anamnesis and clinical course are in complete accordance with the clinical picture described as lower nephron nephrosis. The histologic findings are also in conformity with this, but the changes demonstrated are strikingly slight considering the almost completely suspended renal function. Characteristic are the high values of the ratio I/Tm at the beginning of the disease and the slow change of this ratio, indicative of the fact that the disease has impaired tubular function to a greater degree than glomerular function.

CASE II. This was a twenty-three year old man who, without any preceding recognized disease, had for one year been suffering from frequency of micturition with frothy urine, periodic fatigue and functional dyspnea. Proteinuria was noted one week before admission

to the hospital. The following findings were made in the department: Anemia (hgb. 58 per cent), hypertension (blood pressure 190/100), uremia (blood urea 237 mg. per cent), isosthenuria and considerably reduced clearances. Biopsy of the kidney showed completely and partially

woman who had been suffering from diabetes for fourteen years and was treated with insulin for seven years. For one year proteinuria and decreasing vision had been noted. On admission a mild diabetes was found, with little or no glucosuria although the dose of insulin

TABLE I

KIDNEY FUNCTION IN A CASE OF TUBULAR NEPHRITIS

Case I	Day of Illness	C_{In} ml./min.	C_{urea} ml./min.	C_{PAHA} ml./min.	Tm_{PAHA} mg./min.	$C_{creat.}$ (24 hr.) ml./min.	I/Tm
	13	1.9	1.4	1.5	0.0	1.8	∞
	19	10.3	9.4	.....	0.2	10.7	49.1
	32	36.2	25.1	185	9.6	54.1	3.78
	62	57.8	38.6	392	24.7	73.6	2.34
Normal values:	..	120	75	600	75	100	1.6

Inulin clearance (C_{in}), urea clearance (C_{urea}), p-amino hippuric acid clearance (C_{PAHA}), maximal tubular excretion of p-amino hippuric acid (Tm_{PAHA}), 24-hour endogenous creatinine clearance ($C_{creat.\ 24\ hr.}$) and the ratio $\frac{\text{inulin clearance}}{Tm_{PAHA}}$ (I/Tm), which represents the glomerular activity in relation to the tubular activity. All values corrected to 1.73 m^2 body surface.

hyaline glomeruli with shrivelling and agglutination of the capsular space and thickening of Bowman's capsule, considerable atrophy of the tubules and increase of interstitial tissue and diffuse interstitial cell infiltration, chiefly with lymphocytes. (Fig. 4.) *Histologic diagnosis:* chronic glomerular nephritis.

Functional tests (Table II) showed much reduced values for all functions examined; the ratio I/Tm was somewhat lower than the normal, presumably indicating that the glomeruli were comparatively more injured than the tubules.

The patient was treated with a high-calory diet poor in nitrogen with good effect for six months, after which the uremia suddenly became aggravated and the patient died in a week. Postmortem examination showed chronic glomerular nephritis.

Comment. According to the anamnesis, which revealed no acute precursory stage or preceding tonsillitis, the case must be classified as one of chronic glomerular nephritis (of type 2 according to Ellis's classification). The histologic findings after biopsy corresponded to the postmortem findings. The functional tests seemed to show a slight preponderance of the glomerular injury over injury to the tubules.

CASE III. This was a sixty-two year old

was less than half the dose given a year before. Moderate hypertension and anemia were present.

Ophthalmoscopy showed numerous globular micro-aneurysms and scattered, yellowish-white, fresh cotton-wool exudations; further, there was universal narrowing of the arteries.

Biopsy of the kidney (Fig. 5) showed several hyaline glomeruli with surrounding interstitial connective tissue and atrophic tubules. In several of the glomeruli hyaline precipitations of the Kimmelstiel-Wilson type were seen, embedded in the basal membranes, most of them of the diffuse type, a few, however, being nodular. *Histologic diagnosis: intercapillary glomerulosclerosis (Kimmelstiel and Wilson).* Functional tests (Table II) showed a fairly equal decrease of the functions examined to between a half and two-thirds of normal.

CASE IV. This was a twenty-eight year old woman who because of hyperthyroidism had had a thyroidectomy in 1936 and because of relapse had been operated upon on again in 1940. After the last operation she developed postoperative tetany with serum calcium at a level of 6.4 mg. per cent. She was treated effectively with calcium and A.T. 10. Since 1947 she had been given an ultraconcentrated vitamin D_2 preparation. At the beginning there was

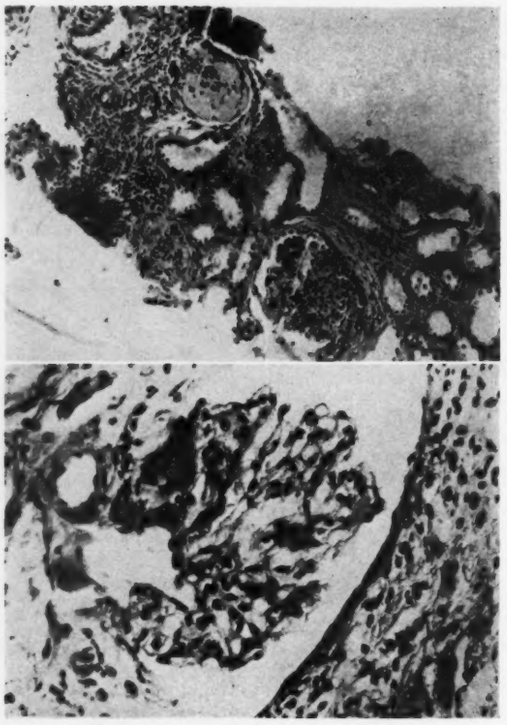

FIG. 4. Chronic glomerular nephritis; completely and partially hyaline glomeruli with shrivelling and agglutination of the capsular space; considerable atrophy of the tubules and increase of interstitial tissue with diffuse interstitial cell infiltration, chiefly lymphocytes; × 140.

FIG. 5. Diabetes mellitus; intercapillary lesion in diabetes mellitus; nodular type; × 370.

control of the serum calcium but later there was no control. For a year before admission the patient had been tired and anemic and was suffering from nausea, vomiting and anorexia. On admission the blood urea was 54 mg. per cent, serum calcium 18.4 mg. per cent, hgb. 67 per cent. Intravenous urography showed no concrements, no calcification of the renal parenchyma and normal excretion of the contrast medium in normal pyelograms. X-rays of the femur and the humerus showed normal structure of the bones. Biopsy of the kidney was made twice at an interval of three weeks. On the first occasion the specimen consisted almost exclusively of medullary tissue (Fig. 6) in which precipitation of calcium was seen in several collecting tubules. A slight diffuse lymphocyte cell infiltration could also be observed. A second specimen consisted of cortical tissue which showed nothing unquestionably abnormal apart from a slight increase of connective tissue and some cell infiltration at the transition to the medulla. *Histologic diagnosis:* renal calcinosis.

Functional tests between the two biopsies (Table II) showed an equal lowering of the functions examined to a little less than half the normal. After discontinuance of administration of vitamin D_2 renal function improved considerably.

Comment. After thyroidectomy a woman who was otherwise in good health developed hypoparathyroid tetany which was treated with an ultraconcentrated vitamin D_2 preparation without control of serum calcium and dose. This resulted in injury to the kidneys, anemia and hypercalcemia. Precipitation of calcium in the kidneys could not be demonstrated by roentgenography but biopsy of the kidney revealed considerable calcium deposits in the collecting tubules.

CASE V. This was a sixty-two year old man who contracted syphilis at the age of twenty-eight years and was treated with inunctions and salvarsan. At the age of fifty-one years the patient was admitted to a neurologic department for tabes dorsalis and Charcot's joints. A year before the present admission severe proteinuria and edema were noted. The condition then progressed until his admission when he had

TABLE II

KIDNEY FUNCTION IN FOUR PATIENTS WITH RENAL DISEASES IN WHOM KIDNEY BIOPSY WAS PERFORMED

Case No.	Diagnosis	C_{In} ml./min.	C_{urea} ml./min.	C_{PAHA} ml./min.	Tm_{PAHA} mg./min.	$C_{creat.}$ (24 hr.) ml./min.	I/Tm
II	Chronic glomerulonephritis	4.1	3.7	21	3.3	6.8	1.22
III	Diabetes mellitus	67.2	52.7	335	24.7	44.8	2.72
IV	Vitamin D intoxication	45.0	27.7	323	31.8	61.9	1.41
V	Amyloidosis	56.6	40.9	288	38.1	63.4	1.48
	Normal values:	120	75	600	75	100	1.6

enormous edema and up to 1.7 per cent of protein in the urine, serum albumin 0.9 gm. per cent, serum globulin 3.4 gm. per cent, blood urea 37 mg. per cent and sedimentation rate 131 mm. The patient lost 10 kg. in three weeks on a diet poor in salt. Biopsy of the kidney (Fig. 7) showed that almost all glomeruli contained subendothelial precipitations which stained red with gentian violet; the proximal convoluted tubules were normal, the distal somewhat dilated containing hyaline casts. *Histologic diagnosis:* kidney amyloidosis.

The functional tests showed a lowering to about half the normal values with almost equal distribution to the glomerular and tubular functions. (Table II.)

Comment. According to the anamnesis and clinical findings the diagnosis of amyloidosis of the kidneys was considered probable, and the biopsy of the kidney confirmed the diagnosis. The functional tests showed no characteristic functional pattern.

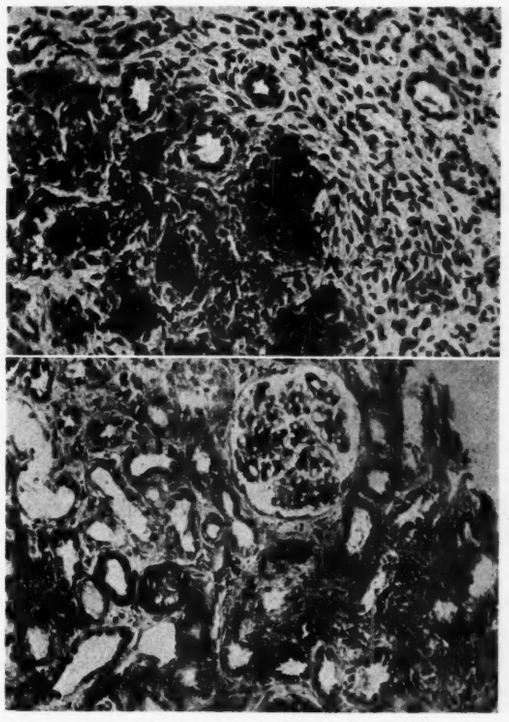

FIG. 6. Hypervitaminosis D; medullary kidney tissue showing calcium precipitation in collecting tubules and interstitial tissue; slight diffuse lymphocyte infiltration; × 140.

FIG. 7. Amyloid disease of the kidney; specific stain (gentian violet); amyloid deposits in glomerulus, tubules and arterioles; × 180.

OBSERVATIONS

The examples given in the preceding pages are sufficient to show what the technic of biopsy of the kidney can afford. It is, of course, of minor importance to decide whether a chronic nephropathy is of one or another form. At present this is of no great importance to therapy. In acute anuria, on the other hand, information about the nature and degree of the renal injury is of great importance and may perhaps decide the choice of method of treatment.

As already mentioned, our knowledge of the pathologic processes underlying the milder cases of anuria or oliguria is very scanty, and in our opinion it will hardly be possible to collect *all* such cases under the diagnosis "lower nephron nephrosis." This term is in itself objectionable insofar as the histologic findings, including those of autopsy materials, show severe interstitial inflammatory changes which do not conform very well to the term *nephrosis.* To this must be added that the injury is not confined to "the lower nephron" alone but also affects the proximal tubules. This appears, among other things, from the fact that the excretion of para-amino hippuric acid, which there is good reason to believe takes place in the proximal tubules, is much impaired, and that alkaline phosphatase, normally present in large quantities in the proximal tubules and in Henle's loops,[7] is lacking or only present in small quantities in "lower nephron nephrosis."[8] On the other hand, a function such as hydrogen ion secretion, which is supposed to take place in the distal portion of the tubules, is apparently unimpaired. At any rate, the urine is, as a rule, highly acid in these patients.

It would undoubtedly not be justifiable to attribute to the localization of the casts any significance in regard to the site of the disease, as the casts must be present in the areas where the urine first attains a sufficient concentration of the substances forming the constituents of the casts.

Therefore, we have for the time being decided on the term *tubular nephritis* to designate the cases of acute renal injury in which relatively normal glomeruli, interstitial inflammation and heme casts in the distal convoluted tubules are demonstrated.

In our opinion it is probable that continued examinations of biopsies of the kidneys of such patients can solve some of the problems in connection with the mechanism of origin and pathophysiology of these disorders. With greater

experience in estimating the changes of the cells and with a more highly developed histologic technic, it will no doubt be possible to obtain valuable information.

It is, of course, quite obvious that by means of this technic we can become enlightened on the condition in only a small portion of the renal tissue, and that this restricts the value of the method. For practical purposes, however, it has appeared that the specimen of tissue removed is sufficiently large to be fairly representative in diffuse renal disorders.

SUMMARY

The authors describe a technic for aspiration biopsy of renal tissue in man. Biopsies from two normal individuals and from five patients with various renal disorders are reported in preliminary form. At the same time determinations of discrete kidney functions were made in these patients.

The authors consider that continued studies of material removed by aspiration biopsy of the kidney may contribute materially to solution of the pathophysiologic problems of the heterogeneous group of renal diseases generally termed "lower nephron nephrosis."

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Review

Angina Pectoris*

A Clinical and Pathologic Correlation

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THE purpose of this study is to gain further insight into the anatomic and functional changes that produce the syndrome of angina pectoris. The roles of hypertensive, valvular and coronary heart disease, which increase the work of the heart or impede coronary blood flow, have attracted our particular attention. The presence, characteristics, distribution and functional significance of the intercoronary collateral circulation in ameliorating the otherwise dire consequences of narrowings and occlusions within the coronary arteries have been closely studied. Finally the importance of extracardiac mechanisms in the production of angina pectoris has also been evaluated.

PATHOLOGIC METHODS

The technic used in injecting and dissecting the heart has been described previously[1] and therefore is stated here briefly. The right and left coronary arteries were injected simultaneously with differently colored, radiopaque lead-agar mass under a pressure of 150 to 200 mm. Hg. The heart was then opened so that the major coronary arteries lay in one plane and a roentgenogram was made. A careful dissection of the arteries was then performed with the film as a guide. Figures 2 and 3 are colored photographs of roentgenograms of hearts with normal and pathologic coronary arteries studied in this way.

The presence or absence of arterial occlusion, narrowing and intercoronary anastomosis is fundamental to the issues discussed in this paper. The technic employed disclosed the narrowings, occlusions and anastomoses in the visualized coronary arteries in each heart. The determination of an anastomotic communication between two coronary arteries was not based on the roentgenogram alone. Anastomotic communications were demonstrated in the subsequent dissection by: (1) the visualization of a mixture of colors in non-occluded vessels; (2) the presence of injection mass in a vessel distal to a complete occlusion or (3) the demonstration between two coronary arteries of a continuous, tinted, endothelial-lined channel filled with injection mass. The distribution of the colors permitted identification of the source of the injection mass and indicated the pathways of the anastomoses.

Although areas of narrowing and occlusion stood out on the film as irregularities in the shadow of the injected mass, the presence, degree and age of the coronary artery narrowings or occlusions were finally decided during the arterial dissection. On dissection the injected arteries were routinely opened down to small branches. The solidified mass found in them as a cast of the size and shape of the lumen facilitated determination of the degree of narrowing or the presence of complete occlusions. The staining of the intima by dye diffused from the mass also aided dissection of small or narrowed vessels. At sites of occlusion, a complete break in the continuity of the lumen was demonstrated and neither mass nor stained intima was found.

The term "occlusion" as used in this communication always denotes complete occlusion. Occlusions were further classified as recent or old on the basis of their gross appearance. In a few instances microscopic studies of the areas of occlusion were made for more accurate estimation of the duration of the occlusive process. In the correlation of the coronary changes with

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angina pectoris, however, acute occlusions are excluded, since angina pectoris had been present for at least one month before death in all the cases used in this study and had, therefore, occurred prior to the deposition of these terminal occlusions.

The degree of narrowing of the coronary arteries was classified in every heart as slight, moderate or marked. Arteriosclerotic changes without any discernible narrowing of the lumen, such as small intimal atheromas, were not regarded as functionally significant and were placed in the normal group without narrowing. "Slight narrowing" refers to hearts with slight but definite constriction of the lumen; "marked narrowing" signifies unequivocal, extreme reduction in the lumen at one or more points in the coronary arterial tree; "moderate narrowing" includes all hearts with intermediate degrees of narrowing. In several hearts the internal diameters of the major vessels were measured by a series of graduated probes, so that the percentage reduction in diameter at areas of narrowing in comparison with immediately adjacent zones was quantitatively determined. Slight narrowing by qualitative estimate was found to correspond approximately with a reduction in diameter of 25 per cent or less; marked narrowing was equivalent to 75 per cent reduction or more.

The presence or absence of cardiac hypertrophy is also of interest when considered in relation to the other findings. Since cardiac hypertrophy may be the result of congestive failure, arterial hypertension, valvular disease, or possibly coronary arteriosclerosis and myocardial fibrosis[2,3] and since two or more of these factors are commonly present, cardiac hypertrophy cannot be attributed with confidence solely to any one of these conditions. In this study a weight of 350 gm. was used as the dividing line between normal and hypertrophied hearts.[4]

After dissection of the coronary arteries in each heart the myocardium, valves and both cardiac surfaces were carefully examined and suitable sections taken for microscopic study. From 500 of the injected hearts in the series a large number of special, individually labelled sections from exactly localized areas of the heart were obtained in order to permit closer correlation of the local histopathology of the myocardium with changes in the coronary arteries.

Instead of presenting colored photographs of the roentgenograms, we have prepared diagrammatic tracings of the coronary arterial tree of the hearts which are used as examples in this paper.

NATURE OF CLINICAL STUDIES

Since the purpose of this study is to gain insight into the clinical consequences of pathologic changes, no case was included unless both adequate clinical and pathologic data were available. Some patients who were admitted to the hospital on several occasions had histories on each admission taken independently by several house officers and fourth-year clinical clerks, and had been questioned, in addition, by visiting staff members. Some patients had been followed in private practice by associates; others had been seen repeatedly over a period of many years in the cardiac clinic of the hospital. In every case utilized in this study a satisfactory injection was completed, an adequate roentgenogram of the injected heart was obtained, and the dissection was carefully performed and described in detail. From a total series of 1,011 unselected autopsied cases in which the hearts were injected by the above technic, adequate clinical observations were available in 905 instances.

We accept the term "angina pectoris" to denote a syndrome consisting of paroxysmal substernal or precordial pain or discomfort of short duration, frequently radiating to the shoulders and inner aspects of the arms, precipitated by exertion, emotion or other states in which the work of the heart is increased, and relieved by rest or nitroglycerin.

Eight cases of angina pectoris of short duration (less than one month before death) were omitted from this study in order to eliminate patients in whom angina pectoris might have been entirely a prodromal manifestation of terminal coronary failure or myocardial infarction. Other types of cardiac pain such as the prolonged pain of coronary failure[5] or of acute myocardial infarction are not considered equivalents of angina pectoris; they will form the subject of other communications.

For purposes of this study, arterial hypertension was considered to be present if either the systolic or diastolic pressure was 150 or 90 mm. Hg, respectively, or higher. We regard the blood pressure observations in this series as subject to guarded interpretation. The readings were made under varied conditions in the out-

patient clinics, by private physicians or in the hospital; they were subject to the many influences that inevitably prevail under these variable circumstances.[6] Although there were repeated blood pressure measurements in almost all the cases, only one observation was made in a few instances. The frequency with which patients exhibit transitory elevated pressures during stress, or conversely, reveal temporary normal levels during convalescence, infection, terminal illness or even simple bed rest serves further to impair the accuracy of conclusions based on observations made over a brief period in the hospital. It is particularly difficult to rule out arterial hypertension in patients who were observed only during or following serious illness such as acute myocardial infarction. In the presence of a marked degree of hypertension these considerations do not weigh so heavily. Nevertheless, analysis of the available measurements of blood pressure permits a reasonable evaluation of the significance of arterial hypertension as an etiologic factor in the pathogenesis of angina pectoris.

In the total series of 905 cases there were thirty-five patients (4 per cent) in whom the usual blood pressure level could not be ascertained because of the considerations discussed above. Of these thirty-five, twelve had angina pectoris; they all showed coronary or valvular disease in addition to the equivocal hypertension. In order to exclude these equivocal instances from groups in which a single etiologic factor might be considered to be the sole cause of angina pectoris, they were considered to have hypertension. This arbitrary decision did not affect the statistical validity* of the results.

RESULTS

Pathologic Aspects of Angina Pectoris

Among the 905 unselected necropsied cases were 185 with a history of angina pectoris. In eight of these the angina was of less than one month's duration. The group of 177 cases with angina pectoris of one month's duration or longer forms the basis of the present study.

The significance of functional and structural cardiac abnormalities in patients with angina pectoris must, however, be appraised in the light of the findings in patients who suffered no such symptom. Among the 720 patients without angina pectoris were forty-nine who had had the pain of myocardial infarction or coronary failure and 671 without any cardiac pain. This group of 671 cases without any cardiac pain serves as the control group to be contrasted with the 177 cases with angina pectoris.

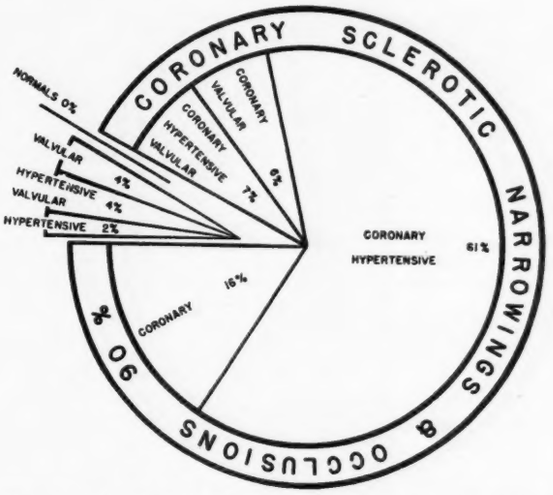

FIG. 1. The etiologic substrate of angina pectoris based on 177 cases.

Our clinical and pathologic studies show that coronary arteriosclerosis, arterial hypertension and valvular heart disease, alone or in combination, form the etiologic substrate of all the cases of angina pectoris. (Fig. 1.) In no instance does angina pectoris exist without such evidence of cardiovascular disease. The majority of the 177 patients (78 per cent) exhibit multiple rather than single etiologies as the basis of their angina pectoris. Furthermore coronary disease is the most common cause, being present in 90 per cent of the entire group.

Coronary Arteriosclerosis. Arteriosclerotic narrowings and occlusions of the coronary arteries were observed in 159 (90 per cent) of the 177 hearts of the patients with angina pectoris. (Fig. 1 and Table 1.) Old occlusions of coronary arteries were present in 108 of these 159 hearts, and coronary artery narrowing without occlusion in fifty-one. In only twenty-eight patients (16 per cent) with angina pectoris did coronary disease occur alone without additional cardiac disturbance.

The cases with coronary disease were divided according to the degree, location and number of occlusions and narrowings found in the coronary arterial tree. From Table 1 it is evident that patients with angina show great variability

* In the statistical treatment of the data in this report, differences of 2.5 times the standard error have been considered "significant."

in the extent of these arteriosclerotic lesions. The group with old occlusions comprised 61 per cent of the cases with angina; in these 108 hearts 312 old occlusions were found, or an average of 2.9 occlusions per heart. A review of all cases in the series with occlusions of the three main coronary arteries disclosed, however, two patients (series No. 701 and 721) who were free of angina pectoris even though hypertension or valvular disease were present in addition to occlusion of all three main coronary arteries.

quantitative estimations of the amounts of fibrosis were made for each section. From these figures the amount of fibrosis in the entire heart was determined. Of the 500 hearts in the entire series in which these special microscopic sections were available, there were 238 with coronary artery narrowing or occlusion, of which ninety were from patients with angina pectoris and 148 from patients without angina. Myocardial fibrosis was present in 90 per cent and intercoronary anastomoses in 88 per cent of the ninety hearts from anginal patients. Although fibrosis and anastomosis were usually found together (80 per cent), in some instances only fibrosis (9 per cent) or anastomosis (7 per cent) was present alone, and in 3 per cent neither occurred. In coronary artery disease angina pectoris, myocardial fibrosis and intercoronary anastomoses all result from myocardial ischemia: the first is a clinical expression, the second a pathologic end result and the third a compensatory response to ischemia. The fact that chest pain, myocardial scarring and collateral channels are not invariably correlated in each heart in no way invalidates the theory that they

TABLE 1

RELATION OF ANGINA PECTORIS TO CORONARY, VALVULAR AND HYPERTENSIVE DISEASE

	Angina Pectoris	Degree of Coronary Artery Disease							
		Normal Coronary Arteries	Narrowings			Occlusions			
			Slight	Moderate	Marked	Branch	1 Stem	2 Stem	3 Stem
Without hypertensive or valvular disease	Present	0	0	4	1	1	10	10	2
	Absent	220	47	32	17	5	12	4	0
	Angina, %	0	0	11	6	17	46	71	100
With hypertension	Present	4	3	9	20	12	32	25	8
	Absent	114	46	33	20	13	14	2	1
	Angina, %	3	6	21	50	48	70	93	89
With valvular disease	Present	7	3	0	3	0	3	1	0
	Absent	37	9	3	1	1	3	0	0
	Angina, %	16	25	0	75	0	50	100	. . .
With hypertensive and valvular disease	Present	7	3	2	3	1	2	0	1
	Absent	15	5	4	2	8	2	0	1
	Angina, %	32	38	33	60	11	50	0	50
Totals	Present	18	9	15	27	14	47	36	11
	Absent	386	107	72	40	27	31	6	2
	Angina, %	4	8	17	40	34	60	86	85

Marked and moderate coronary artery narrowing alone may produce angina pectoris, but slight coronary narrowing *per se* is apparently an inadequate stimulus for the production of this symptom. All nine patients with angina pectoris whose hearts showed only slight coronary artery narrowing also had hypertension or valvular disease.

To clarify further the mechanism underlying episodes of paroxysmal cardiac pain in patients with coronary artery occlusions, myocardial fibrosis was studied in patients with and without angina pectoris. All the special, individually labelled microscopic sections were reviewed and

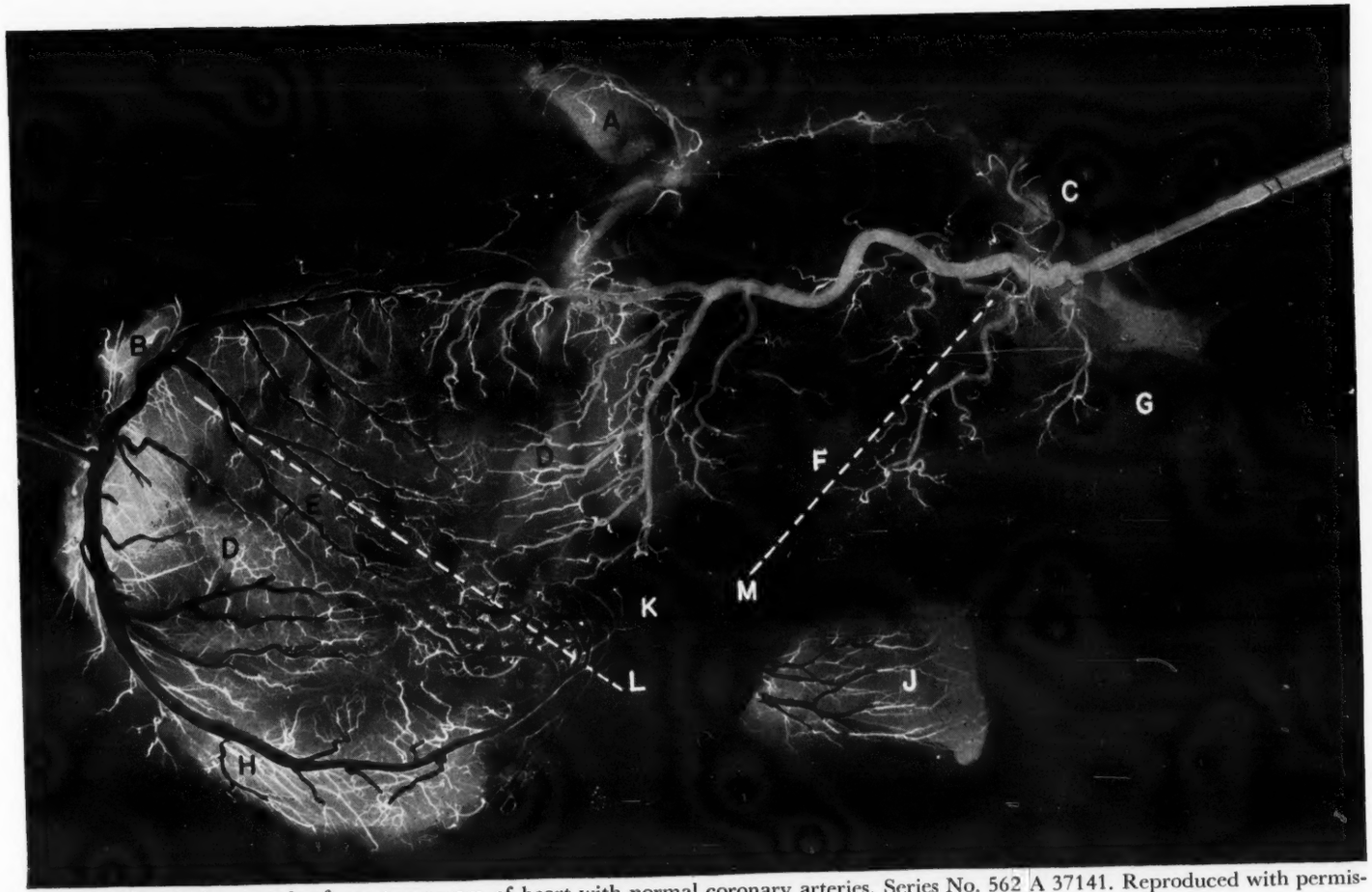

FIG. 2. Colored photograph of roentgenogram of heart with normal coronary arteries. Series No. 562 A 37141. Reproduced with permission of the publishers, The C. V. Mosby Company, from the *Am. Heart J.*, 15: 551, 1938.[1]

Angina Pectoris. A Clinical and Pathologic Correlation. By Paul M. Zoll, M.D, Stanford Wessler, M.D. and Herrman L. Blumgart, M.D.
American Journal of Medicine, September, 1951

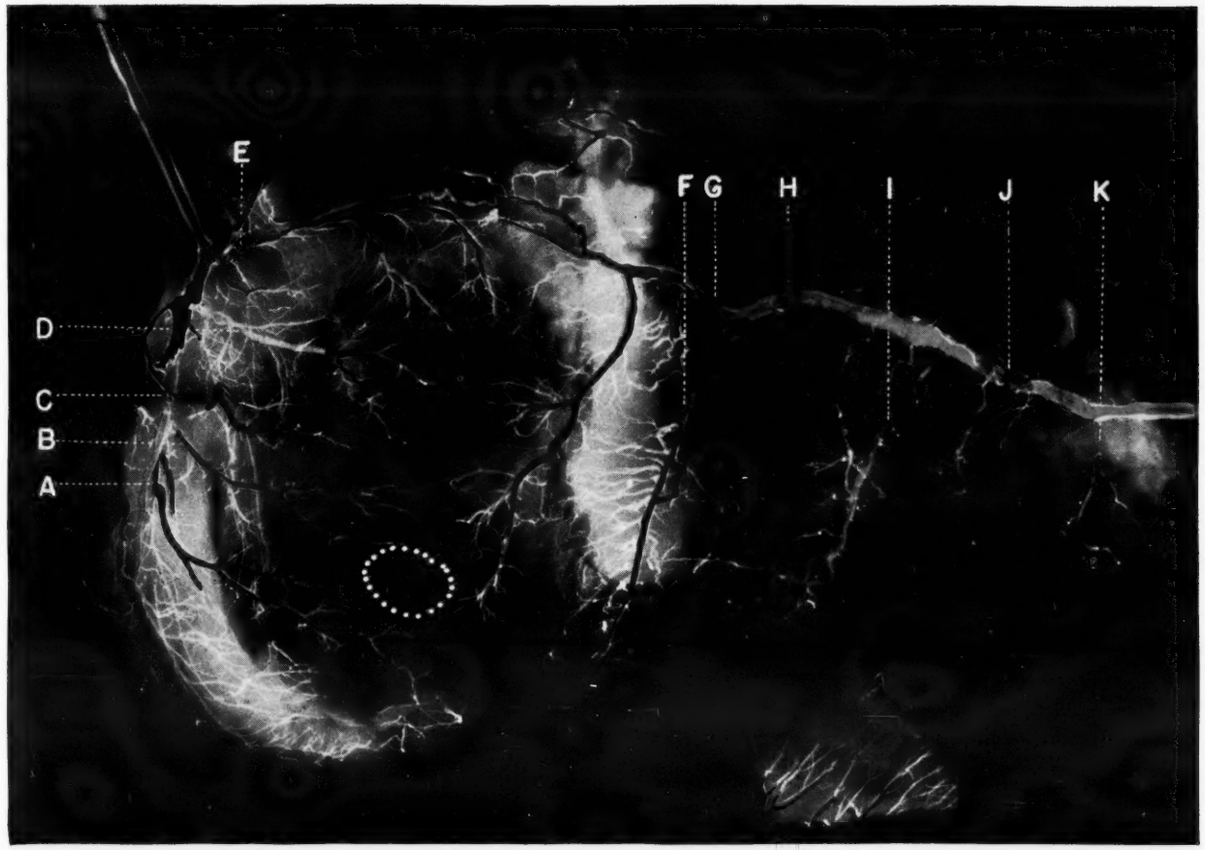

FIG. 3. Colored photograph of roentgenogram of injected diseased heart. Detailed clinical and pathologic data of this case appear in Case IV. Reproduced with permission of the publishers, The C. V. Mosby Company, from the *Am. Heart J.*, 19: 5, 1940.[20]

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all result from myocardial ischemia; differing attendant circumstances and varying degrees and duration of ischemia will determine its effect.

The incidence of both fibrosis and anastomosis was higher in anginal patients (90 and 88 per cent) than in the non-anginal groups (51 and 58 per cent) with coronary disease. This difference is simply a reflection of the greater extent of coronary artery disease and its myocardial consequence in the hearts of patients with angina.

Since all hearts with old occlusion are found to have anastomoses by the Schlesinger technic,[4] the absence of angina or myocardial fibrosis in some patients who showed old occlusions may be accounted for by the propitious development of intercoronary collateral circulation. It is, however, impossible to be certain from the pathologic details in a given heart (i.e., coronary occlusions, anastomoses, myocardial fibrosis) whether the patient had angina pectoris during life.

Individual case reports are presented in this paper to emphasize specific clinical and pathologic aspects of angina pectoris. They are not meant to represent a typical sampling of the entire group; this type of information is given in the statistical data.

Several examples of angina pectoris on the basis of coronary artery occlusion and narrowing are presented. Three show occlusions in all three main stems, one shows occlusions in two main coronary arteries and one shows occlusions in one main coronary artery. The sixth case shows marked and the seventh case shows moderate coronary artery narrowing.

CASE 1. (Fig 4.) (Series No. 74 A 42–73). *Angina pectoris and clinical acute myocardial infarction five years before death; hypertension for ten years; death from congestive failure. Nine old occlusions involving all main coronary arteries; rich collateral circulation. Extensive myocardial fibrosis and hypertrophy but no localized infarction.*

A fifty-eight year old man, H. S., a patient of Dr. L. Wolff, entered the hospital two weeks before death because of increasing chest pain and shortness of breath. Hypertension, 190 to 230 systolic and more than 100 diastolic, had been present for at least ten years.

Five years before death there began frequent episodes of severe, vise-like precordial pain which also radiated to both shoulders and down the left arm to the elbow. They were usually under ten minutes in duration, occurred often on exertion or emotion and particularly at night, and were relieved by nitroglycerin or rest. Nine weeks later he was hospitalized with an acute myocardial infarction. This attack was characterized by prolonged severe cardiac pain

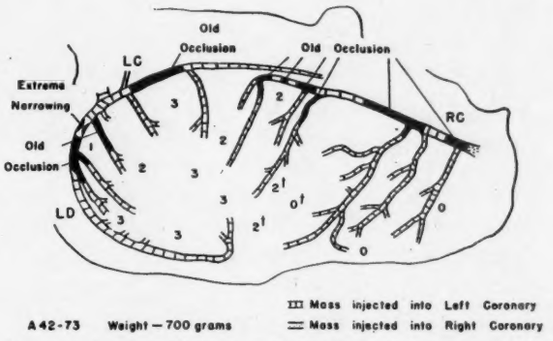

FIG. 4. Case 1. Diagram of injected heart. Numbers refer to degree of microscopic fibrosis in localized areas of the myocardium on scale of 0 to 3. Symbol (†) indicates acute necrosis. Sections from interventricular septum are not shown in the diagram.

unrelieved by morphine, persistent singultus, hypotension of 110/80, leukocytosis and progressive electrocardiographic changes of an acute posterior wall infarction. Following recovery he used as many as 100 nitroglycerin tablets a week. Three years before death the patient was hospitalized again with a second episode of severe, crushing, prolonged pain which was thought to be another infarction. There were no new electrocardiographic changes but sedimentation rates were elevated. Congestive failure appeared at this time, required repeated hospitalizations and progressed rapidly in the last year before death. The blood pressure during this year averaged about 130/80.

Physical examination on the last admission showed wheezing respiration, distended neck veins and peripheral edema. The heart was enlarged, the rate was rapid and irregular and there was a rough systolic murmur at the apex. Bubbling rales and wheezes were heard throughout the lung fields, there was dullness at the right base and the liver was large and tender. Blood pressure was 130/70. Laboratory studies showed erythrocyte sedimentation rates ranging from 0.25 to 0.8 mm./minute.* Electrocardiograms showed paroxysmal auricular fibrillation or partial A-V block, and intraventricular con-

* Rourke-Ernstene method with normal range 0.1 to 0.4 mm. per minute.[7]

duction delay, with a pattern suggesting incomplete left bundle branch block.

Frequent nocturnal angina and severe nocturnal dyspnea with pulmonary edema were serious problems during the patient's stay, but there was some temporary slight improvement until he suddenly expired on the nineteenth hospital day.

At necropsy there was evidence of chronic passive congestion in the liver, lungs and kidneys.

The heart was markedly hypertrophied, weighing 700 gm. There were no valvular lesions. The myocardium showed extensive diffuse myocardial fibrosis and slight spotty necrosis on gross and microscopic examination, which included seventeen special, labelled microscopic sections. There was, however, no definite area of old or fresh infarction.

The entire coronary tree was filled with blue mass from the left coronary artery by way of intercoronary arterial anastomoses. Nine old complete occlusions were found involving all three main coronary arteries and many of the primary branches. When the heart was opened, blue injection mass was also found in the left ventricular chamber.

Comment. This case is presented as an example of angina pectoris in the presence of very extensive coronary arterial sclerosis with occlusions in all the main coronary stems. In addition marked arterial hypertension had been present for many years. The mere survival of this patient in the face of so much coronary disease indicates the extent to which intercoronary anastomoses may substitute for obstructed pathways. In this heart with nine old occlusions and extensive anastomoses all semblance of an end arterial system was lost.

The extensive collateral circulation was not, however, completely adequate. Insufficient coronary blood flow was manifest clinically in frequent angina pectoris and pathologically in extensive diffuse myocardial fibrosis and necrosis. Although the development of collateral channels provided detour pathways for coronary blood flow, the pressure gradient through them must have been greatly reduced[8] so that irrigation of some parts of the myocardium became insufficient.

Study of the special, labelled microscopic sections showed marked, diffuse fibrosis throughout the left ventricle. Myocardial necrosis in varying stages of development was also found in the left ventricle. Even a minor episode of myocardial ischemia, which may be manifess clinically as an anginal attack, may result in irreversible damage to a few myocardial fibert with progression to focal, microscopic necrosis and subsequent fibrosis. It is because of repeated, focal episodes of myocardial ischemia and necrosis of this sort that many patients with angina pectoris, but without clinical acute myocardial infarction, show persistent, slightly elevated sedimentation rates.

The progressive congestive failure which supervened during the last year of the patient's life may be regarded as a late consequence of the replacement of heart muscle by fibrous tissue. With continued necrosis and fibrosis the efficiency of the heart as a pump may be impaired and cardiac output reduced.[9]

Clinical episodes of "acute myocardial infarction" are usually expected to result in well localized, homogeneous areas of infarction. If, however, collateral circulation has developed prior to these episodes, clearly circumscribed infarction may be prevented and instead a variable amount of spotty necrosis may occur as the pathologic basis of the same clinical picture of infarction. Furthermore, with the same clinical syndrome of "acute infarction," including electrocardiograms, the findings in the coronary arteries also vary markedly. Instances of acute infarction may be associated with narrowing, fresh occlusion or old occlusion of the coronary arteries.[10] In contrast to the opinion of Master[11] it is our experience that the clinical diagnosis of extensive myocardial necrosis can be made with reasonable accuracy, whereas the exact age and number of coronary artery occlusions cannot ordinarily be determined during life.

The history of two episodes of severe, prolonged cardiac pain in this patient six and three years before death is pertinent in this regard. These episodes of prolonged pain may have marked the formation of one or more of the occlusions in the coronary arteries with ischemia and scattered necrosis in the myocardium. It is thus of particular interest that the electrocardiograms in this patient's first hospitalization showed a pattern characteristic of acute posterior wall myocardial infarction. Although the intraventricular conduction delay with a pattern suggesting incomplete left bundle branch block interfered with the accurate electrocardiographic diagnosis of infarction[12] at the time of the second episode of pain, the clinical

picture and the elevated sedimentation rates suggested another infarction.

Another finding of interest was the extravasation of injection mass from the coronary arteries into the left ventricular chamber. Leak from the coronary arteries into the ventricular cavity is unusual with the injection technic employed. It may result from an artificial postmortem tear of a coronary artery or arteriole or from antemortem damage of the myocardium and a coronary vessel by ischemia or necrosis. If a rupture of a small coronary artery internally into a cardiac chamber occurs before death it might well constitute a terminating accident as catastrophic as a typical complete, through and through myocardial rupture with cardiac tamponade. Small internal ruptures of this nature may occur with survival of the patient in instances of tears of papillary muscle from acute infarction or severe trauma. It is difficult to demonstrate such an "internal rupture" without an injection technic; even with this procedure its presence antemortem is not clearly established in this case.

CASE II. (Fig. 5.) (Series No. 71 A 42–7). *Angina pectoris for eleven years and hypertension for fourteen years; myocardial infarction six years before death, no congestive failure; death from cerebral hemorrhage. Four old occlusions involving all main coronary arteries; rich collateral circulation; old infarction at posterior base of left ventricle.*

L. S. L., a seventy year male patient of Dr. A. S. Freedberg, had had hypertension for fourteen years and angina pectoris for eleven years. The angina consisted of short episodes of precordial oppression which radiated to the upper part of the left arm; the attacks occurred several times daily on walking or emotion and were relieved by rest.

Six years before death the patient suffered a typical attack of acute myocardial infarction with prolonged pain, fever, collapse and electrocardiographic changes of posterior wall infarction. In addition, he experienced two episodes of coronary failure nine years and one and one-half years before death, with prolonged cardiac pain and collapse, but no signs of myocardial necrosis and no electrocardiographic changes characteristic of infarction. On hospitalization for the first of these three episodes physical examination showed no cyanosis nor congestive failure. The heart was enlarged, the sounds were of good quality, regular and rapid. The blood pressure was 200/115. He was finally hospitalized with a massive cerebral hemorrhage and died in two days.

At necropsy the heart was hypertrophied and weighed 440 gm. There was a small old healed infarct in the posterior basal portion of the left ventricle. The valves were normal.

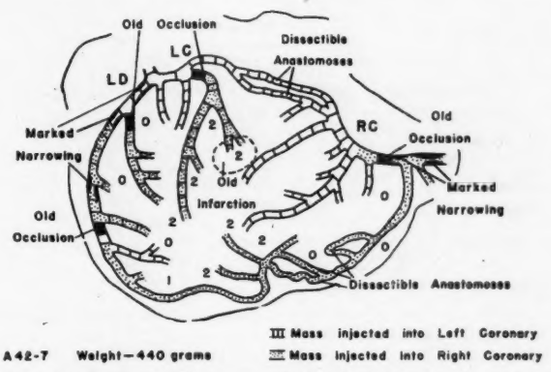

FIG. 5. Case II. Diagram of injected heart. Numbers indicate degree of microscopic fibrosis in localized areas of the myocardium on scale 0 to 3. Sections from interventricular septum are not shown in diagram.

The coronary arteries showed pronounced arteriosclerosis, with widespread narrowing and four old occlusions, one in each main coronary artery and one in a primary branch of the left anterior descending coronary artery. A well developed anastomotic circulation with many grossly dissectible channels was present.

Comment. This case is presented as an example of angina pectoris on the basis of extensive coronary disease plus arterial hypertension. The three episodes of prolonged cardiac pain (coronary failure and myocardial infarction) represent episodes of prolonged inadequacy of the coronary circulation and may have marked instances of rapidly occurring coronary occlusion which outstripped the development of a compensatory collateral circulation.

The duration of life after the onset of angina pectoris and after the episode of myocardial infarction is longer than usual in this series. Despite the long duration and marked degree of coronary disease and arterial hypertension, and the occurrence of myocardial infarction and myocardial fibrosis, congestive failure did not appear. Congestive failure is usually late and less prominent than cardiac pain in coronary heart disease unless widespread fibrosis has occurred.

The broken circular line in Figure 5 indicates the limits of the healed myocardial infarction in the posterior wall as it appeared on gross

pathologic examination. On microscopic study of the many labelled sections from this heart, however, diffuse fibrosis of moderate amount was found to extend over a much wider area of the left ventricle. Estimations of extent and uniformity of acute or healed myocardial in-

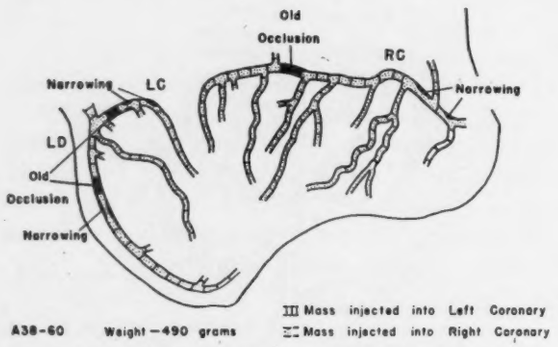

FIG. 6. Case III. Diagram of injected heart.

farction by gross examination were often found to be at variance with microscopic study. Microscopically, areas of old or acute damage are much less uniform in content and more irregular in outline than would appear grossly. For this reason unsupported macroscopic impressions of myocardial infarction must be accepted with caution.

CASE III. (Fig. 6.) (Series No. 2 A 38–60). *Angina pectoris ten years; congestive failure three months; no hypertension or valvular disease; occlusion of right femoral artery with gangrene of leg; death from postoperative shock and arrhythmia. Occlusions of all three main coronary arteries; extensive intercoronary collateral circulation; slight myocardial fibrosis; no old or recent myocardial infarction.*

A man, W. G., sixty-seven years old, was admitted to the hospital ten days before death because of progressive pain in the right lower leg of one month's duration.

For ten years the patient had experienced precordial and substernal pain on effort which was relieved by rest. During the last eight years the patient had been under the care of Dr. S. L. Gargill and at no time had had any episodes of prolonged chest pain or any elevation of blood pressure. Three and one-half months before death the patient had an uneventful prostatectomy. Several weeks after this operation intermittent sharp pain appeared in the right leg, at first on effort and subsequently at rest. The pain became progressively more severe and the leg became swollen, cold and cyanotic. The cardiac rhythm was normal and there was no evidence of congestive failure until one month before death. Subsequently, however, increasing signs of congestive failure appeared. Physical examination on admission, ten days before death, showed dyspnea, orthopnea, distended neck veins, numerous fine rales at the bases of both lungs and cardiac enlargement. The heart beat was grossly irregular, with a ventricular rate of 130 and a pulse rate of 90. The blood pressure was 110/75. The right leg was cyanotic, cold and pulseless. The electrocardiogram showed auricular fibrillation with a ventricular rate of 160. The patient was immediately digitalized. Gangrene of the right leg became more pronounced, and amputation of the right leg was performed under spinal anesthesia on the ninth day following admission. Postoperatively the patient remained stuporous except for short intervals and the heart rate rose to 150. Approximately eight hours after operation the heart beat became regular and very rapid. The respirations became irregular and gasping and the patient expired twenty-eight hours after operation.

At necropsy thrombosis of the right femoral artery was found.

The heart was hypertrophied weighing 490 gm. There was a slight amount of patchy, irregularly distributed fibrosis of the left ventricle without evidence grossly or microscopically of old or fresh infarction. There were antemortem thrombi in the left ventricle and both auricles. The valves were normal. There were extensive narrowing and a single old occlusion in each of the three main coronary arteries. There were no fresh occlusions. The anastomotic circulation was extremely rich.

Comment. Despite the extensive coronary obstruction in this case, the resulting ischemia produced only angina pectoris and some scattered fibrosis. The extensive collateral circulation stimulated by this same myocardial ischemia was undoubtedly responsible for the absence of old or recent infarction. It was this probably that was responsible for the fact that frank congestive failure did not appear until the last month of life and then only after gangrene of the right leg was present. The progressive gangrene of the right lower extremity with pain and infection increased the metabolic demands of the body and contributed to the development of congestive failure by increasing the cardiac work. Death resulted from postoperative shock and cardiac arrhythmia.

CASE IV. (Fig. 7.) (Series No. 6 A 36–96). *Angina pectoris ten years; no congestive failure; death following prolonged cardiac pain and collapse. Old occlusions in two main coronary arteries; fresh occlusions in right coronary artery; rich collateral circulation; old myocardial infarction and extensive fibrosis; no acute infarction.*

M. L., a fifty-three year old patient of Dr. M. F. Lesses, had experienced attacks of angina pectoris for ten years; the pain was precordial, slight, infrequent and was precipitated by exertion. Three years before admission it became more severe and radiated down the left arm. Rest and nitroglycerin afforded relief. Although the attacks became more frequent and severe in the last two weeks of life, the patient worked continuously until the day of entry. Finally he suffered persistent, severe, squeezing, substernal pain which was not relieved by nitroglycerin. After several hours of pain he visited his physician and was immediately sent to the hospital. Physical examination showed slow, grossly irregular cardiac rhythm, occasional rales at the bases of the lungs and a blood pressure of 118/80. The patient's distress persisted unrelieved by repeated injections of morphine. After nineteen hours of pain the patient complained of marked increase in its intensity and became cold, clammy and pulseless; he expired three hours later.

At necropsy the heart weighed 350 gm. and showed no valvular lesions. The myocardium showed diffuse fibrosis and an old healed infarction on the obtuse border of the left ventricle. There was no acute myocardial infarction.

Extensive arteriosclerosis was present in the coronary arteries. In addition to widespread narrowing there were nine old occlusions involving the left anterior descending and left circumflex main stems and six primary branches. The main right coronary artery was also occluded at three sites by a recent thrombus and two emboli from it. Since these emboli were adherent to the intima, they could not have been dislodged from the parent thrombus by the injection mass but must have been formed before death. There was a well developed anastomotic circulation by which all the coronary vessels were well injected with mass distal to both old and recent occlusions.

Comment. This heart affords a striking example of how complicated, extensive and unpredictable the compensatory circulation may be. Angina pectoris had been present for ten years as a result of the marked coronary sclerosis, without other etiologic substrate. In this heart there were nine sites of old occlusion and three fresh ones. Nevertheless, an extensive and complicated anastomotic compensatory circulation sufficient to sustain life had developed.

The increasing frequency and severity of

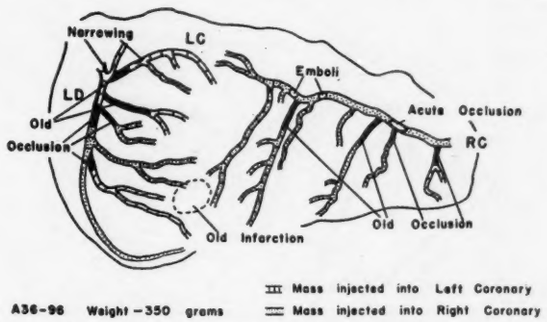

FIG. 7. Case IV. Diagram of injected heart.

angina during the final two weeks of life and the development of severe, persistent pain twenty-two hours before death were evidently caused by marked narrowing and, finally, sudden, thrombotic occlusion of the right coronary artery. The absence of pathologic evidence of recent infarction, despite the fact that the pain had persisted for twenty-two hours, suggests that the patient might have survived even this episode if secondary embolism from the parent thrombus had not occurred. The exacerbation of pain and collapse three hours before death may have signalled this event. The terminating attack of prolonged cardiac pain due to acute coronary occlusion without myocardial infarction may be classified as an episode of coronary failure.

It is of interest that a small area of old infarction existed in a portion of the myocardium most remote from the larger vessels. Since there was no clinical history of prolonged cardiac pain before the terminal episode, this area of fibrosis may represent simple coalescence of small areas of fibrosis in a poorly nourished portion of the heart.

Thus this case re-emphasizes the fact that anastomotic circulation, while sufficient to meet ordinary needs, does not provide a wide margin of safety; exertion and emotion may precipitate myocardial ischemia with resultant angina pectoris and myocardial fibrosis. Over a period of time this sequence may lead to extensive, localized fibrosis which is indistinguishable from a massive, healed infarct.

Coalescent fibrosis in this way offers an addi-

tional explanation for the occasional finding of a healed pathologic infarct without its clinical counterpart. Other causes for the absence of a clinical story of infarction include a failure to elicit a history or a misinterpretation of its clinical manifestations. Implicit in this discussion is the view that a large healed myocardial infarction is similar to a microscopic area of fibrosis in every respect except size: their mechanism and significance are similar.

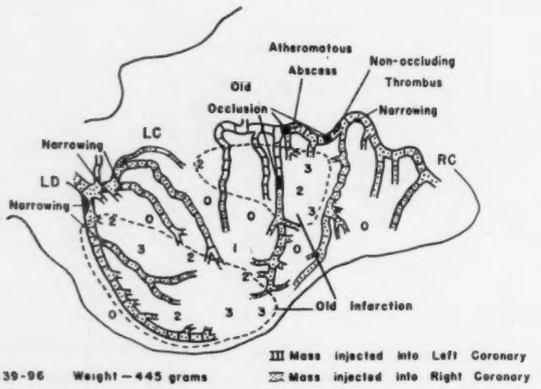

FIG. 8. Case v. Diagram of injected heart. Numbers indicate degree of microscopic fibrosis in localized areas of the myocardium on scale 0 to 3. Sections from the interventricular septum are not shown in the diagram.

CASE V. (Fig. 8.) (Series No. 25 A 39–96). *Angina pectoris for eighteen months following acute myocardial infarction; congestive failure for two weeks during terminal illness only; no hypertension; death from carcinoma of the pancreas. Three old occlusions in right coronary artery; rich collateral circulation; old infarctions at apex and posterior base of the left ventricle; no acute myocardial infarction.*

A man, S. F., aged sixty-five, a patient of Dr. L. Wolff, was hospitalized nineteen months before death with a typical, acute anterior wall myocardial infarction which had its onset during severe unusual effort of lifting a heavy carton. He had never previously suffered any cardiac pain, dyspnea, palpitation, edema or cough and had always been active and vigorous. Thereafter, he experienced definite substernal pressure of short duration on walking fast, with immediate relief by rest. There were no other episodes of prolonged or severe chest pain.

Two weeks before death he re-entered the hospital because of progressive, painless icterus. Physical examination showed deep jaundice, cardiac enlargement and a slow, regular rhythm; A2 was accentuated; there were no murmurs and the blood pressure was 130/80. A few rales were heard at the lung bases and there was marked peripheral edema. A cholecystogastrostomy was performed but the patient died five days later with peritonitis and cholemia.

At necropsy carcinoma of the head of the pancreas with biliary obstruction and acute peritonitis was found.

The heart was hypertrophied weighing 445 gm. Special, labelled microscopic sections were taken from twenty-one locations in the myocardium. Two separate areas of old, healed infarction, one anteriorly and the other posteriorly, were found. No fresh myocardial infarction was seen. The valves were normal. Chemical determinations of the collagen content[13] of various sections of heart muscle were found to correlate closely with the microscopic fibrosis.

The coronary arteries showed marked arteriosclerosis with several areas of marked narrowing in all three main stems and three complete old occlusions, two in the main stems and one in a primary branch of the right coronary artery. There were also a fresh, adherent but non-occluding thrombus and an acute, ulcerated atheromatous abscess immediately proximal to the old occlusions in the right main coronary artery. A rich anastomotic circulation was found with complete filling of the entire coronary tree with injection mass.

Comment. This case is presented particularly as an example of angina pectoris due to coronary arteriosclerosis with complete occlusions in a single main coronary artery. Other possible etiologic bases for angina pectoris, such as hypertension or valvular disease, were absent.

The massive, healed infarction found at the apex appears to be the pathologic basis for the clinical episode of acute anterior wall myocardial infarction which occurred nineteen months before death. The precipitation of the attack of severe cardiac pain immediately upon severe, unusual exertion is of interest in view of recent discussions of the relation of exertion to the onset of acute myocardial infarction.[14–19] In this series many factors, such as operation, circulatory collapse, exertion and infection, have been associated with the onset of acute infarction.

In this heart with apical infarction old occlusions were found only in the right coronary artery. The infarction may have been produced by acute occlusion in the right coronary artery, or by prolonged ischemia resulting from severe exertion in the presence of previous occlusions

in the right coronary artery and marked narrowing in the other coronary arteries. The occurrence of an anterior left ventricular infarct secondary to occlusions in the right coronary artery represents an example of "infarction at a distance."[20] The fact that "infarction at a distance" can occur indicates that the original end arterial system has been replaced by a richly anastomotic coronary arterial circulation, so that heart muscle may depend for its blood supply upon distant vessels.

The second old infarction at the posterior base of the heart may have occurred at the same time since only one clinical episode of infarction was experienced. The simultaneous occurrence of the two infarcts is understandable on the basis of the anatomy and pathology of the coronary arteries as representing a single infarction divided in two by a corridor of normal muscle. Irregular distribution of myocardial damage is often evident on a smaller scale in hearts with previously developed anastomoses in the form of scattered patchy necrosis or fibrosis rather than uniform, homogeneous infarction. Such irregularity in extent and location of myocardial damage depends upon the anatomy of the individual heart with its own particular relationships between sites of occlusion and anastomotic vessels. The intervening zone of normal muscle between the two areas of old infarction can be seen to be well supplied by coronary vessels in which there is relatively little obstruction. The smaller basal posterior wall infarction was not represented in the electrocardiograms, either because it was overshadowed by the larger apical infarction, because it was in a silent area not reflected on the electrocardiogram, or because it did occur, indeed, at some other time without any clinical manifestations.

Since the fresh thrombus found in this heart was immediately adjacent and proximal to one of the complete occlusions in the right coronary artery and did not narrow the lumen markedly, it is to be considered the result rather than the cause of the terminal shock and death which were of non-cardiac origin.[21] The ulcerated plaque found in the right coronary artery was also of interest since it, too, may have resulted from the diminished coronary blood flow which was secondary to shock, cholemia and peritonitis. Degenerative changes secondary to local ischemia may occur in the arterial walls just as in the myocardium.

CASE VI. (Fig. 9.) (Series No. 127 A 41–69.)

Angina pectoris and arterial hypertension for seven years; no congestive failure; death from acute myocardial infarction. Marked narrowing in three main coronary arteries and recent occlusion in right coronary artery; rich collateral circulation; minimal myocardial fibrosis; acute myocardial infarction.

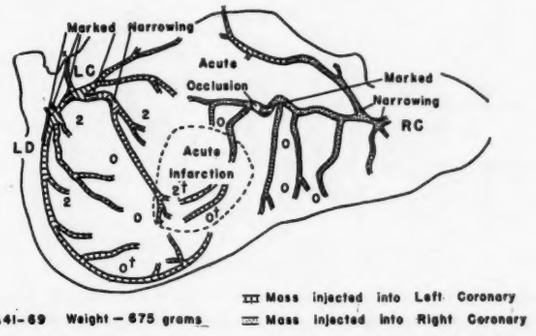

FIG. 9. Case VI. Diagram of injected heart. Numbers refer to degree of microscopic fibrosis in localized areas of the myocardium on scale of 0 to 3. Symbol (†) indicates acute necrosis. Sections from interventricular septum are not shown in the diagram.

A. J. H., a physician aged sixty-five years, entered the hospital with an acute myocardial infarction and died in three days. Generalized, familial xanthomatosis had been present for thirty-seven years and a cholecystectomy was performed for cholelithiasis seven years before death. At that time a history was obtained of constricting precordial pains of a few minutes' duration which were precipitated by exertion or emotion and relieved by rest. Physical examination showed xanthomas and a blood pressure of 190/90. Subsequently, the chest pains became more severe, usually radiated to the right shoulder and arm, and occurred two to three times daily; they were relieved by nitroglycerin but not by rest alone.

Ten months before death the patient was hospitalized with an episode of severe precordial pain of several hours' duration which required morphia for relief. There were no evidences of shock or congestive failure, no signs of tissue necrosis and no significant electrocardiographic changes. This episode was therefore considered one of coronary failure.[5] The blood pressures ranged between 148/76 and 185/110, and the electrocardiograms showed a typical pattern of left ventricular hypertrophy. The serum cholesterol was 624 mg. per cent.

After this episode the patient restricted his activities but still suffered occasional anginal attacks. Finally, he was seized with severe, prolonged constricting precordial pain which

was relieved only temporarily by morphia. After two days he was hospitalized because of rising pulse rate, falling blood pressure and recurrent chest pain. On physical examination the lungs were clear. The heart was enlarged, the rhythm was regular and rapid, the sounds

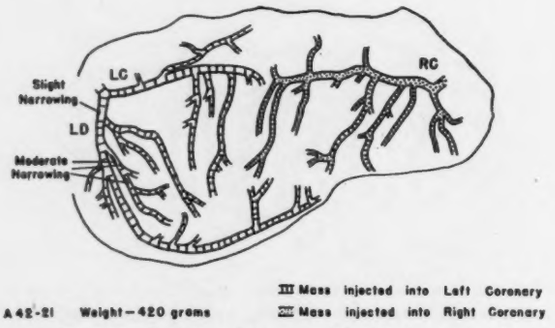

FIG. 10. Case VII. Diagram of injected heart.

were of good quality and there was a rough systolic murmur all over the precordium. The blood pressure was 110/65. The white blood count was 17,000 and the electrocardiogram showed bundle branch block (probably right bundle) and acute posterior wall infarction. Severe chest pain recurred and the patient died in three days in pulmonary edema and shock.

At necropsy multiple xanthomatosis and marked widespread atherosclerosis were found.

The heart was markedly hypertrophied weighing 675 gm. In the twelve special, labelled microscopic sections focal myocardial fibrosis and acute infarction were found. The valves were normal.

There was extensive arteriosclerosis with extreme narrowing in all three main coronary arteries and several branches. A fresh occlusion, caused by an edematous atheromatous plaque, was present in the distal third of the right main coronary artery. There was a well developed anastomotic circulation with one grossly dissectible communication.

Comment. This patient suffered every type of cardiac pain in the spectrum from angina pectoris through coronary failure to myocardial infarction. The basis of this pain was coronary artery narrowing plus hypertension. The narrowing was very marked and involved all main coronary arteries and obviously had greatly reduced the coronary blood flow. On the one hand, the arterial hypertension and cardiac hypertrophy increased the myocardial requirement for blood and exaggerated the relative inadequacy of the coronary supply. On the other hand, rich interarterial coronary anastomoses were present; they resulted from the myocardial ischemia and tended to reduce the amount of fibrosis.

The coronary arteriosclerosis was only a part of the extensive atherosclerosis found in this patient. Generalized arteriosclerosis and particularly coronary disease is commonly found in patients with hereditary xanthomatosis and hypercholesterolemia.

CASE VII. (Fig. 10.) (Series No. 62 A 42–21.) *Angina pectoris for seven years; no myocardial infarction, hypertension or congestive failure; death from pulmonary tuberculosis, pneumonia and sepsis. Moderate narrowing in one coronary artery; no occlusions; no collateral circulation; no myocardial fibrosis; no valvular disease.*

A man, L. T., fifty-four years old, a patient of Dr. B. Alexander, was admitted to the hospital because of two days of recurrent hemoptysis, fever, dyspnea and malaise.

Fourteen years prior to entry the patient was found to have diabetes mellitus and one year later active pulmonary tuberculosis. During the subsequent twelve years, however, the patient was well enough to work as a shipyard driller. Seven years prior to entry he noted the onset of precordial choking pain on walking hills, climbing stairs or becoming excited. These episodes never lasted more than ten minutes and were invariably relieved by rest. During all these years the patient was under close supervision in the out-patient department of another hospital. There had never been any hypertension, cardiac arrhythmia, congestive failure or re-activation of the tuberculous lesions.

Physical examination showed a dyspneic, flushed man with slight cyanosis. The chest was emphysematous with dullness and diminished breath sounds at both apices and coarse, moist rales at the left base. The heart sounds were distant with a regular rhythm at a rate of 100. No murmurs or thrills were noted. The blood pressure was 150/80. The fingers and toes were clubbed. The urine contained albumin and sugar and the hemogram was normal. A roentgenogram showed apical tuberculosis and pneumonia, and tubercle bacilli and pneumococci were found in the sputum. The patient failed to respond to therapy and expired on the twelfth hospital day with extreme dyspnea and hyperpyrexia of 106°F.

Necropsy revealed very extensive, old healed tuberculosis at both apices and active tuber-

culosis with cavitation and pneumonia throughout both lung fields.

The heart was hypertrophied weighing 420 gm. There was no fibrosis or infarction in the nine special, labelled microscopic sections of the myocardium. The valves were normal.

The main stem of the left anterior descending coronary artery showed one area of slight narrowing and one branch revealed three areas of moderate narrowing. The remainder of the coronary tree was normal. No anastomotic collateral circulation was demonstrated.

Comment. This patient had angina pectoris for seven years with a cardiac substrate of narrowing in one coronary artery. This case illustrates the small degree of coronary obstruction that may be required to produce angina if other important contributory factors are present, such as the extensive pulmonary disease observed in this patient. The clubbed fingers and extensive pulmonary disease found at necropsy suggest that active pulmonary tuberculosis may have accelerated the appearance of angina pectoris by reducing pulmonary oxygenation and by increasing cardiac work. The slight degree of coronary arteriosclerosis is of interest in the presence of long-standing diabetes which is ordinarily considered to accelerate the arteriosclerotic process.[22]

The complete absence of fibrosis in this heart supports the concept that the ischemic process in angina pectoris may be completely reversible and may not cause any demonstrable organic damage. In spite of the presence of enough coronary sclerosis to produce angina, interarterial anastomoses were not demonstrated. This patient is one of the few with angina pectoris due to coronary artery disease whose hearts showed neither myocardial fibrosis nor coronary anastomoses. Of the ninety hearts from which multiple sections were taken from patients with angina pectoris due to coronary disease, there were only three without fibrosis or anastomosis. Angina pectoris, intercoronary arterial anastomoses and myocardial fibrosis are all produced by varying degrees of myocardial ischemia. Therefore, they often appear together in the same case but are not directly interrelated. Perhaps if a collateral circulation had developed in this heart, angina pectoris might not have occurred.

Valvular Heart Disease. Of the 177 patients with angina pectoris there were thirty-six (20 per cent) with valvular heart disease. The etiology of the valvular lesions in the thirty-six patients with angina pectoris was luetic aortic insufficiency in three, arteriosclerotic aortic stenosis in eight and rheumatic mitral or aortic lesions in twenty-five. Only seven (4 per cent) were unassociated with hypertension or obstructive coronary sclerosis. The valvular lesions in these seven cases were aortic stenosis in three hearts, mitral stenosis in two and combined aortic insufficiency and mitral lesions in two; the etiology of the valvular disease was rheumatic in five and arteriosclerotic in two cases. Because mitral stenosis alone is an unusual cause of angina pectoris in this series, one of them is presented in detail.

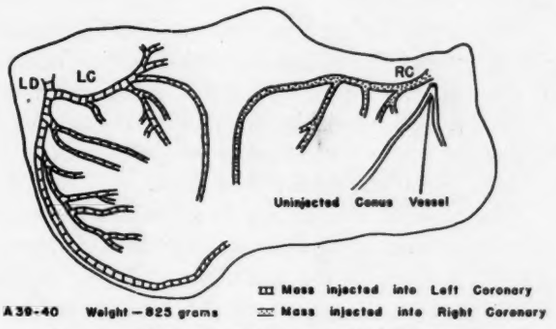

FIG. 11. Case VIII. Diagram of injected heart.

CASE VIII. (Fig. 11.) (Series No. 176 A 39–40). *Angina pectoris four years and congestive failure eleven years; mitral stenosis with auricular fibrillation; total thyroidectomy six years before death; death from pneumonia and congestive failure. Normal coronary arterial tree with no narrowing, occlusion or anastomosis; no myocardial fibrosis or infarction.*

A man, H. G., aged twenty-eight, was admitted to the hospital because of congestive failure and pneumonia. From the age of five he had experienced exertional dyspnea with progressive diminution in his cardiac reserve. By the age of seventeen he had frank congestive failure with repeated hemoptysis, tachycardia and occasional syncope. During the next five years the patient had six severe attacks of congestive failure and finally became completely bedridden. From this time he was observed closely and treated in the Medical Research Department of the Beth Israel Hospital. Frequent physical examinations showed signs of marked congestive failure, cardiac enlargement, double mitral murmurs and rapid auricular fibrillation. The blood pressure was 100/55.

Because of the uncontrollable congestive failure and complete incapacitation, total thyroid-

ectomy was performed at the age of twenty-two. Following operation the patient experienced a pronounced increase in his cardiac reserve. He was able to walk one to two miles daily and became gainfully employed as a baker's assistant. Myxedema was controlled by thyroid medication.

Four years before death the patient first noted severe precordial pain on exertion lasting only a few minutes, relieved by rest and associated with dyspnea. Five weeks before death an episode of severe substernal pain lasting twelve hours began when the patient strained at stool.

The patient was finally hospitalized because of progressive congestive failure and a pneumonic process in the right upper lobe. Treatment was of no avail and the patient expired thirty-four days after hospital entry.

Necropsy examination of the lungs revealed extensive bronchopneumonia. The liver showed cardiac cirrhosis.

The heart was markedly hypertrophied, weighing 825 gm. The myocardium was entirely normal on gross and microscopic examination, including seventeen special, labelled microscopic sections. The collagen content of the left ventricle, septum, right ventricle and right auricle was normal, with values of 1.09, 1.03, 1.22 and 3.74 gm. per cent, respectively.[13] The mitral valve showed typical fish-mouth stenosis.

The coronary arteries showed slight atheromatosis without occlusion or narrowing. No interarterial coronary anastomoses were found. The conus artery[23] found in this heart was not filled by way of anastomotic channels.

Comment. Since coronary artery narrowing or occlusion and arterial hypertension were absent, the only basis for the cardiac pain in this patient is the mitral stenosis with cardiac hypertrophy. Mitral stenosis, uncomplicated by other valvular lesions or by other cardiac disturbance, is a very uncommon cause of angina pectoris;[24–26] in our series it occurred twice.

Several mechanisms have been suggested whereby angina pectoris may be produced in patients with mitral stenosis.[27–31] The marked pulmonary disorder together with pulmonary congestion in mitral stenosis results in diminished oxygen saturation of the blood.[29] The diminished cardiac output because of the obstructing mitral valve reduces the blood flow through the coronary arteries. The resistance to blood flow offered by the stenotic valve may also increase cardiac work, lead to hypertrophy and greatly increase the metabolic requirements of the heart. Narrowing of the left coronary ostium by traction from the distorted anterior mitral cusp, the mechanism advanced by Hochrein,[28] was not found in this heart. All these processes may produce relative or absolute insufficiency of coronary blood flow with resultant myocardial ischemia and angina pectoris. In this case the unusual myocardial hypertrophy of 825 gm. suggests that increased myocardial requirement for blood was a prominent factor.

The sequence of the cardiac manifestations in this patient is considerably different than in Case 1. In this patient with mitral stenosis congestive failure was incapacitating and very early in onset, whereas angina pectoris was relatively mild and appeared only after the congestive failure had been present for seven years. Indeed, if total thyroidectomy had not resulted in improvement in the congestive failure and permitted more activity, it would seem likely that angina might not have appeared.

In patients with valvular disease angina pectoris is less common than congestive failure, usually occurs late in the course of the disease long after the onset of congestive failure and is of correspondingly more ominous prognostic significance; in patients with coronary disease the reverse relation between angina pectoris and congestive failure is found. (Fig. 16.) Limitation of activity from congestive failure may delay or prevent entirely the appearance of angina.

Despite the combined presence of congestive failure and angina pectoris in this patient there was no myocardial fibrosis. Fibrosis is less likely to appear in anginal patients with valvular or hypertensive disease than with coronary disease;[32] when it does occur in valvular disease, it is often predominantly perivascular in location, as a residual of old inflammatory lesions.

The absence of increased intercoronary anastomoses in this case is in accordance with our observations[4] that anastomoses occur with much greater frequency in the presence of marked coronary narrowing or occlusion than when only valvular disease or myocardial hypertrophy is present. There is, furthermore, no direct relation between intercoronary anastomosis and angina pectoris; both result from myocardial ischemia or anoxia, the one as a compensatory response and the other as a clinical expression of it. As a result they are often found together in the same patient. The development of intercoronary anastomoses, however, tends

to increase coronary blood flow and thereby prevent or delay the appearance of angina pectoris.

Finally, the absence of significant coronary disease is of interest in this patient since postoperative myxedema with elevated cholesterol levels had been present for six years. On the basis of this and other similar cases, myxedema with hypercholesterolemia does not necessarily accelerate the arteriosclerotic process in the coronary arteries.[33]

Arterial Hypertension. Of the 177 patients with angina pectoris there were 132 (75 per cent) with arterial hypertension. In only four (2 per cent), however, was the hypertension the sole etiologic factor.

Three of these four hearts were hypertrophied. The fourth case (Series No. 146) was a patient with hypertension for twenty-five years in whom blood pressure readings of 180/100 were repeatedly obtained during the last year of life. In this case, nevertheless, the heart weighed 347 gm. which is below what we have taken as the lower limit of cardiac hypertrophy. It is therefore the only instance in the entire group of 177 cases with angina pectoris in which pathologic examination of the heart might be considered normal. One of these four cases is given as an example.

CASE IX. (Fig. 12.) (Series No. 70 A 41–96.) *Angina pectoris and hypertension for six years; congestive failure for nine months; no myocardial infarction; death from congestive failure and uremia. No coronary sclerosis; extensive intercoronary anastomoses; marked myocardial hypertrophy; no myocardial fibrosis or necrosis; no valvular disease.*

A woman, L. S., fifty-five years old, a patient of Dr. K. C. Rosen, was admitted to the hospital for the third time two months before death.

Six years prior to entry she developed a tight sensation in the upper substernal area precipitated by exertion and cold or windy weather. These episodes were promptly relieved by nitroglycerin. Hypertension was also noted at this time. Two years later she was seen by a cardiac consultant, Dr. S. A. Levine, who confirmed the diagnosis of angina pectoris and recorded a blood pressure of 165/100. Since then the patient continued to show a fluctuating hypertension, the highest diastolic level recorded being 110.

Eleven months before death the patient was hospitalized because of severe congestive heart failure. This was partially controlled with appropriate therapy and the patient was sent home on limited activity. Two months before death she developed a severe productive cough, nightly paroxysmal dyspnea and intractable congestive failure for which she was hospitalized. Examination at that time showed cyanosis and

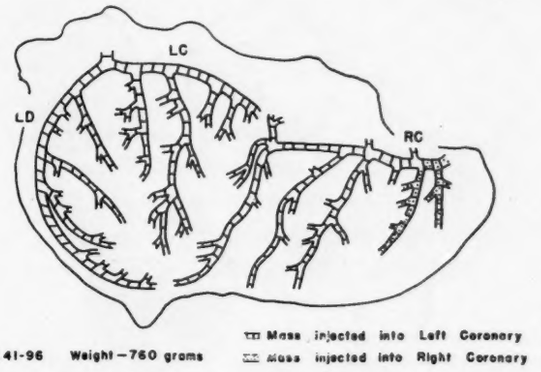

FIG. 12. Case IX. Diagram of injected heart.

orthopnea; slight lid-lag, exophthalmos and a large nodular goiter; distended neck veins, basal rales, a tender liver edge six fingers below the costal margin and marked pitting edema of the extremities. The cardiac impulse was diffuse, the heart sounds muffled and the rhythm regular. A paradoxical pulse and blood pressure of 110/100 were noted.

Urinalysis showed heavy albuminuria and many white cells. The blood counts were normal; the NPN was 49. Although pericardial effusion was seen in the roentgenogram, a pericardial tap yielded only small amounts of clear yellow fluid. Oliguria developed, the NPN rose to 99, ventricular tachycardia supervened and the patient expired on the seventh hospital day.

At necropsy there was thrombosis of the right renal artery with multiple right renal infarcts, marked narrowing of the left renal artery with an atrophic left kidney and bilateral hydronephrosis. The thyroid gland contained a struma lymphomatosa (Hashimoto's disease). There was marked congestion of the viscera.

The pericardial sac was normal. The heart weighed 760 gm. and was markedly hypertrophied. No fibrosis or infarction was found in the twelve special, labelled microscopic sections of the myocardium. The valves were also normal.

The entire coronary arterial tree was free of narrowing and occlusions. There were extensive intercoronary arterial anastomoses.

Comment. This case represents one of the few instances in the series in which hypertension

alone formed the etiologic substrate of angina pectoris. Like the anginal pain the intercoronary anastomoses found in this heart may be regarded as a response to the increased metabolic requirements of the hypertrophied myocardium. This collateral circulation was not sufficient, however, to prevent myocardial ischemia when the cardiac work was further increased by exertion.

FIG. 13. The incidence of angina pectoris in patients with single etiologic types of heart disease.

Although the patient had hypertension for six years of a degree sufficient to produce angina pectoris and congestive failure, no coronary artery disease nor myocardial fibrosis was found. Hypertension by itself only rarely produces cardiac pain (Figs. 1 and 13); some caution should nevertheless be exercised in making a clinical diagnosis of coronary artery disease to account for angina pectoris when mechanisms such as valvular disease or hypertension are present.

Relative Significance of Single Etiologic Factors in Angina Pectoris. The preceding observations indicate that in this study coronary, hypertensive and valvular heart disease form the etiologic substrate of angina pectoris. To appraise the relative significance of these factors, however, it is necessary to determine the incidence of angina pectoris in each of these three types of heart disease. For this purpose the cases with and without angina pectoris which showed only one of these three types of heart disease form particularly pertinent groups. (Fig. 13.) The 848 cases used for this analysis consist of 177 patients with angina pectoris of one month's duration or longer, and 671 control patients without angina pectoris or other cardiac pain.

The group of cases without coronary, hypertensive or valvular heart disease is presented first. In the series of 848 cases there are 220 in which these three factors are absent; not a single instance of angina pectoris was found in this group.

In the series of 848 cases there are 101 with coronary artery narrowing and forty-four with coronary artery occlusion in the absence of arterial hypertension or valvular disease. The incidence of angina pectoris is 5 per cent in the group showing only coronary narrowing and 52 per cent in the cases with coronary occlusion.

In the series of 848 cases there are forty-four in which valvular disease occurs without arterial hypertension or coronary artery disease. Of this group in which valvular disease is the only cardiac disturbance seven patients had angina pectoris, an incidence of 16 per cent.

The relative significance of different valvular lesions in the production of angina pectoris was studied. Valvular cases with arterial hypertension but none with coronary disease were used for this purpose, since arterial hypertension was found to be a minor factor and coronary disease a prominent factor in the etiology of angina pectoris. Of the valvular cases without coronary disease there were fourteen cases with angina and fifty-two cases without angina. Angina is more frequent in aortic than in mitral disease but this difference is statistically significant only in the comparison of aortic stenosis and mitral stenosis: four of five patients with aortic stenosis had had angina pectoris whereas three of fourteen with mitral stenosis had angina.

Finally, there were 118 patients with arterial hypertension in whom no significant coronary or valvular disease was found; four of them (3 per cent) had angina pectoris. This low incidence in patients with hypertension alone was not altered significantly by eliminating slight or borderline hypertensives from the group. When the criterion for hypertension was raised to a diastolic level of 100 mm. Hg, the incidence of angina pectoris in this group was 6 per cent (four of sixty-seven cases).

The 3 per cent incidence of angina pectoris in arterial hypertension may be compared with 16 per cent in valvular disease, 5 per cent in coronary artery narrowing and 52 per cent in hearts with coronary occlusions. (Fig. 13.) No patient in the entire series had angina pectoris in the absence of all three etiologic factors.

The preëminent role of coronary sclerosis in the production of angina pectoris can be estimated in still another way. All 848 cases were classified in the order of increasing degree of

arterial obstruction by coronary narrowing and occlusion without regard to hypertension or valvular disease. The incidence of angina pectoris shows a progressive increase (Fig. 14 and bottom row Table 1) with the exception of the group of cases in which occlusions were present only in branches of the coronary arteries. This exception emphasizes the significance of the location of lesions in the coronary arteries: complete obstruction in branches of coronary arteries is evidently of less functional importance than severe narrowing in more strategic locations.

The addition of arterial hypertension and valvular disease to coronary arterial narrowing and occlusion is associated with an increase in the frequency of angina pectoris. (Table 1.) The significance of these factors in producing angina in patients with coronary disease is most evident in patients in whom the coronary disease is relatively mild. In patients with slight coronary narrowing, for example, angina pectoris was found only in the presence of hypertensive or valvular disease. In patients with moderate or marked narrowing the addition of hypertension and valvular disease was also associated with a significant increase in the incidence of angina. In the presence of coronary artery occlusions, however, the addition of hypertensive or valvular disease did not show a significant rise in the incidence of angina pectoris.

In brief, the importance of coronary artery disease in the production of angina pectoris is demonstrated by the fact that it is the most common of the three etiologic factors, that more than half of patients with coronary artery occlusion experience angina, and finally, that with increasing degrees of coronary obstruction, the incidence of angina pectoris rises.

Clinical Aspects of Angina Pectoris

Sex and Age. Among the 177 patients with angina the sex ratio (male/female) is 2.5/1. This preponderance of males was significantly greater than among the control group of 671 patients without angina in which the sex ratio was 1.4/1.

The age of patients with angina pectoris at the time of death ranged from twenty-one to eighty-four years. Only seven patients with angina died before forty; all of them had valvular heart disease.

The age of patients at the onset of angina ranged from seventeen to eighty-three years, with an average of fifty-eight years. Patients with coronary disease as the sole etiology of angina pectoris did not develop angina before the age of forty, whereas its onset in patients with hypertension or valvular disease was not infrequent in the third and fourth decades. The youngest patient with angina pectoris, with onset at the age of seventeen, had rheumatic aortic stenosis (Series No. 175).

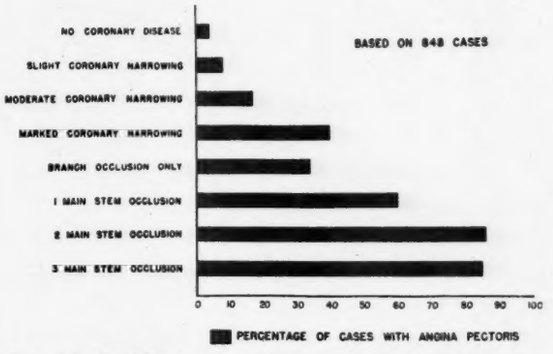

FIG. 14. Incidence of angina pectoris in relation to increasing degree of coronary artery obstruction.

Duration of Angina Pectoris. The duration of life after the onset of angina pectoris in this series ranged from one month* to nineteen years, with an average of 4.2 years. The serious prognostic import of angina pectoris in this group is evident in Figure 15: one-third of the patients were dead within one year after the onset of angina, almost half (47 per cent) were dead within two years, and the five- and ten-year mortality rates were 72 and 92 per cent, respectively. Indeed, the first two years after the onset of angina pectoris are of critical prognostic importance in that the mortality curve flattens out thereafter.

The mortality curve for angina pectoris differs according to the underlying etiology. It is significantly longer in coronary and shorter in valvular heart disease. (Figs. 16 and 17.) Of fourteen patients with valvular disease without coronary sclerosis ten (71 per cent) were dead within two years and all were dead five years after the onset of angina pectoris. Among 136 anginal patients with non-valvular heart disease (i.e., coronary sclerosis with or without hypertension) only 43 per cent were dead within two years and 69 per cent within five years.

Mechanism of Death. Of the patients with angina pectoris in this series 60 per cent suc-

* It will be recalled that eight patients with angina pectoris of less than one month's duration before death are not included in this analysis.

cumbed to cardiac disease. In them the mechanism of death consisted of acute myocardial infarction, prolonged myocardial ischemia, congestive failure, syncope, arrhythmia, subacute bacterial endocarditis, acute pulmonary edema or cardiovascular collapse. In the remaining

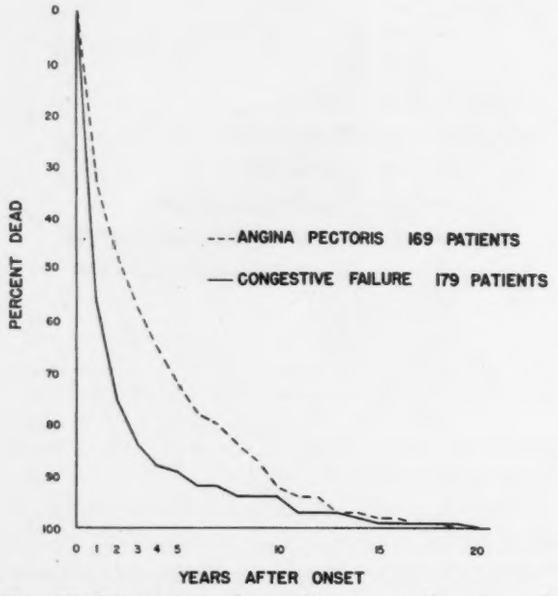

FIG. 15. Comparison of mortality curves after onset of angina pectoris and congestive failure in the total series.

40 per cent of the anginal patients death was attributed to non-cardiac causes, which may be regarded as interrupting the natural course of the cardiac disease. It is realized that in some of the cases mechanisms such as congestive failure, pulmonary edema or circulatory collapse may have contributed to death which was primarily on the basis of non-cardiac disease. Although less cardiac disturbance and shorter duration of angina pectoris might have been expected in the group whose cardiac disease was interrupted by an unrelated death, no differences between the two groups were found in the duration of angina pectoris, in the underlying etiologic substrate or even in the extent of coronary artery obstruction.

Prognostic Significance of Congestive Heart Failure. Among the 848 cases in this series congestive failure occurred in 227. As was done with angina pectoris, forty-three cases of congestive failure of less than one month's duration were omitted from this analysis in order to eliminate patients in whom the failure might have been merely an incident in the terminal illness. In the present analysis these 184 cases with congestive failure are compared with the 177 with angina pectoris; in ninety both of these syndromes co-existed. The incidence of congestive failure was significantly greater than angina pectoris in uncomplicated arterial hypertension (14 vs. 3 per cent) and in uncomplicated valvular disease (48 vs. 15 per cent) but was similar in coronary disease (12 vs. 17 per cent).

Inspection of the mortality curves for congestive failure and angina pectoris (Fig. 15) indicates the graver prognostic import of the former. This impression is supported by statistical analysis of the data. Division of the cases with congestive failure according to etiologic types of heart disease yielded groups with small numbers of cases from which few conclusions concerning the relation of congestive failure to angina pectoris could be made with statistical validity. Statistically significant differences, however, were noted between the non-valvular coronary and the non-coronary valvular groups. (Figs. 16 and 17.) Inspection of these figures reveals that in coronary disease congestive failure offers a poorer prognosis than angina pectoris, whereas in valvular disease angina is the more ominous symptom.

About half (51 per cent) of the anginal patients in this series developed congestive failure of one month's duration or longer. As might be expected from Figure 15, when failure occurs the prognosis of the patient with angina pectoris becomes worse. Thus 82 per cent of such patients were dead within two years of the onset of their cardiac decompensation.

In only twelve of the ninety anginal patients with congestive failure did decompensation appear before angina. This group consisted largely of valvular heart disease.

The amount of myocardial fibrosis in each heart with multiple sections was quantitated. Marked fibrosis was present in 17 per cent of the hearts of the anginal group without congestive failure, whereas among those with failure the incidence of marked fibrosis was 41 per cent.

Although angina pectoris and congestive failure frequently occur in the same patient and auricular fibrillation is frequent in patients with congestive failure, the co-existence of auricular fibrillation and angina pectoris is said to be uncommon. In this series, however, auricular fibrillation was found in eighteen (10 per cent) of the 177 anginal patients. In one additional

case (Series No. 63) angina occurred during an episode of paroxysmal fibrillation.

Clinical Episode of Myocardial Infarction. Since it was our purpose to study the significance of healed infarction in anginal patients, only patients with the onset of their infarction at least two months prior to death were included in this portion of our investigation. In this respect our study of the relationship of myocardial infarction to angina pectoris differs from other reports.[34,35] Among the 848 cases in this series an episode of intercurrent myocardial infarction occurred in sixty-six. Among these sixty-six patients with intercurrent infarction there are fifty-three with angina pectoris. Thus of the anginal patients in this series about one-third (31 per cent) developed intercurrent infarction. In them the duration of angina ranged from two months to nineteen years and was similar to that among the remaining anginal patients without healed clinical infarction. Furthermore, in this series the life expectancy following recovery from the first episode of myocardial infarction was not significantly different from that following the onset of angina pectoris in patients without intercurrent infarction. Finally, the frequency of congestive failure was not significantly greater in anginal patients with a clinical history of infarction (58 per cent) than in those without such a history (46 per cent).

In fifty patients with both angina and healed infarction the date of onset of each syndrome was known. In no patient did the angina disappear following infarction. In seventeen patients the angina preceded the infarction, in eleven it followed infarction and in twenty-two both syndromes appeared simultaneously. The rate of survival following angina was significantly better for the group in which angina preceded infarction. If, however, survival time were measured from the first appearance of cardiac pain, whether angina or infarction, no difference in duration was found in these groups. These considerations give further support to the observation that a history of myocardial infarction and angina pectoris are of equivalent prognostic significance.

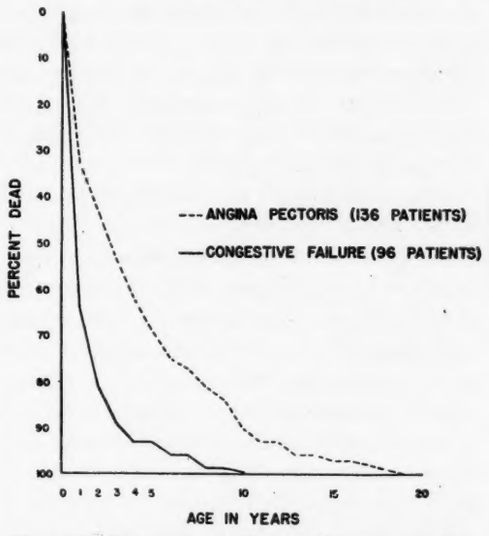

FIG. 16. Comparison of mortality curves after onset of angina pectoris and congestive failure in non-valvular coronary disease.

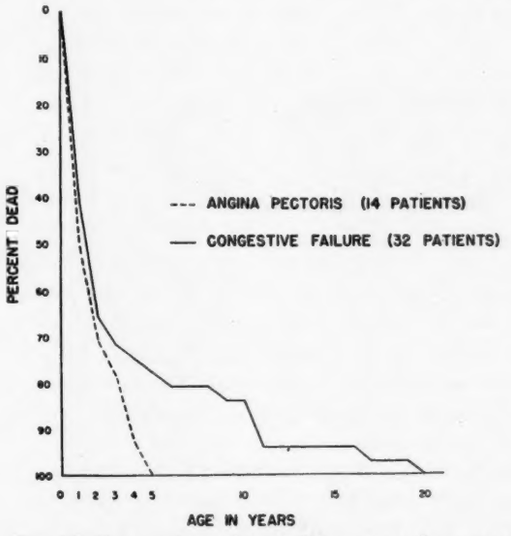

FIG. 17. Comparison of mortality curves after onset of angina pectoris and congestive failure in non-coronary valvular disease.

The similarity in prognosis for anginal patients with and without intercurrent infarction came as somewhat of a surprise to us. It is, of course, entirely possible that a larger series would show that patients with healed infarcts have a poorer prognosis. Nevertheless, review of the multiple microscopic sections of the hearts of all patients with coronary disease and cardiac pain has offered some support for these observations. Most of the anginal cases without infarction showed fibrosis. Many exhibited large amounts of localized and diffuse scarring consistent with the pathologic diagnosis of extensive fibrous myocarditis or healed infarction which had not been suspected clinically. The similarity in the total amount of myocardial fibrosis in the hearts of patients with and without intercurrent infarction supports the observation that prognosis for life is not significantly different in the two

groups. Since congestive failure reflects in part the extent of myocardial fibrosis, the similar frequency of congestive failure in anginal patients with and without intercurrent infarction is not surprising.

In summary, our data indicate that a history

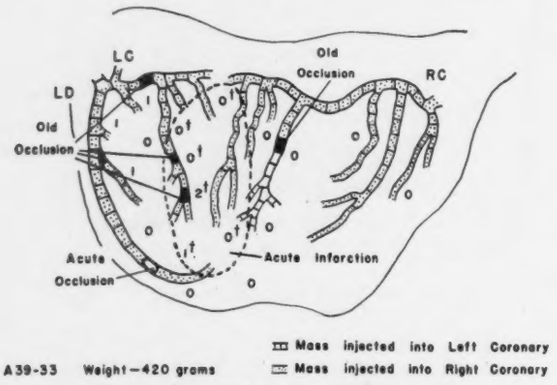

FIG. 18. Case x. Diagram of injected heart.

of recovery from a single episode of myocardial infarction is of the same prognostic significance as a history of angina pectoris. Thus when the physician elicits from a patient a past history of myocardial infarction, he should attach the same significance to it as to a history of angina pectoris: he should expect the same duration of life and the same frequency of congestive failure. Again, the additional knowledge of a history of a single myocardial infarction does not alter the prognosis of a patient with angina pectoris. It is understood that these observations refer to episodes of myocardial infarction from which the patient has recovered. The immediate prognosis of an acute attack of myocardial infarction is, of course, much more ominous than that of an anginal episode.

Analysis of Angina Pectoris of Long (Ten Years) and Short (One Year) Duration. The small groups of patients with angina pectoris of long and short survival are of particular interest; in them one might expect to find the factors which affect favorably or unfavorably the course of angina pectoris. Of the 177 patients in this series with angina twenty-three (13 per cent) lived ten years or more after the onset of this symptom. In contrast there were fifty-five patients (31 per cent) who died within the first year of angina. There was no striking difference in the sex or age at onset of angina between the two groups.

The pathologic substrate of angina was similar in the two groups except that hypertensive and valvular disease with slight or no coronary narrowing occurred much more frequently among the short survival than the long survival group (22 vs. 4 per cent). This finding is consistent with the observations already made on the relative gravity of angina in valvular disease as compared with coronary disease. The amount of coronary artery disease, however, showed a wide variation in both groups, ranging from occlusions in all three main coronary arteries to slight or no coronary narrowing. No difference was found between the extent of myocardial fibrosis in the two groups.

A clinical history of recovery from myocardial infarction did not appreciably shorten the duration of life after the onset of angina. Nine of the twenty-three (22 per cent) patients with long-standing angina gave such a history compared with sixteen (31 per cent) of the fifty-five patients with angina of short duration. This analysis confirms the observation previously made on the entire series that a history of recovery from myocardial infarction does not alter the prognosis of angina pectoris.

Finally, the patients with long survival after angina did not differ significantly from those with short survival in the frequency of congestive failure (57 per cent vs. 43 per cent). Once congestive failure had occurred, however, long survival for the anginal patient was rare.

Role of Other Factors in the Production of Angina Pectoris. There are a number of factors that may precipitate or aggravate angina pectoris by increasing the work of the heart or by reducing myocardial blood supply. In this series these included effort, emotion, infection, anemia, thyrotoxicosis and tachycardia. Although the role of these conditions cannot be clearly delineated in every patient, there are several cases in this study in which, for example, angina pectoris appeared or increased with the development of tachycardia or hyperthyroidism and disappeared when the cardiac and metabolic rates returned to normal. In each instance, however, underlying heart disease was subsequently demonstrated at necropsy. We therefore believe that a diagnosis of angina pectoris is tantamount to a diagnosis of organic heart disease; furthermore, in 90 per cent of anginal patients coronary artery disease is the cause. A case is presented to illustrate the role of one of these special factors.

CASE X. (Fig. 18.) (Series No. 154 A 39–33). *Angina pectoris for fifteen years with marked aggravation by thyroid medication; myxedema for two*

years; death from paroxysmal ventricular tachycardia. Five old and one fresh occlusions in coronary arteries; extensive intercoronary anastomoses; acute myocardial infarction and slight myocardial fibrosis; calcific aortic stenosis with cardiac hypertrophy.

A sixty-nine year old woman, E. McK., entered the hospital for regulation of her metabolic level. For fifteen years she had noticed severe vise-like precordial pain radiating frequently to the left shoulder, elbow and wrist. The pain was of short duration (two to seven minutes), occurred on exertion or nervousness and was relieved by nitroglycerin. Two years before admission there was marked diminution of physical and mental activity, hoarseness, dry coarse skin and hair and progressive weakness. No manifestations of congestive failure appeared. One week before admission a diagnosis of spontaneous myxedema was made and the patient was started on dessicated thyroid, 1½ gr. daily. After three days of this therapy, however, she suffered several spontaneous episodes of severe precordial pain and the medication was stopped.

Physical examination showed coarse hair, dry, thickened skin, mask-like facies, thinning of the outer eyebrows and thick tongue. The lungs were clear and there was no peripheral edema. The heart was enlarged to the left; a loud blowing systolic murmur was heard at the aortic area and the aortic second sound was diminished; the blood pressure was 140/80.

Laboratory studies showed a normochromic anemia (62 per cent hemoglobin), elevated blood cholesterol, slow circulation time and rapid sedimentation rate. The basal metabolic rates varied between −18 and −29 per cent. X-ray of the chest showed moderate enlargement of the heart and pulmonary congestion. Electrocardiograms showed inverted T waves in leads I, II and IV, frequent premature ventricular contractions and finally ventricular tachycardia.

For the first two weeks in the hospital thyroid medication was omitted and the cardiac pain subsided. Thereafter thyroid was tried several times in courses of gradually increasing doses, from 0.1 to 3 gr. With increasing dosage, exacerbations of frequent severe angina pectoris recurred, so that the thyroid had to be reduced or omitted on several occasions, even though there was no significant change in the basal metabolic level. On the sixty-fifth hospital day a paroxysm of ventricular tachycardia at a rate of 160 occurred which subsided temporarily after quinidine therapy but recurred later in the day. During this episode the patient had no pain and felt well; after several hours of tachycardia, however, she suddenly collapsed and expired within a few minutes.

Generalized arteriosclerosis and atrophy of the thyroid were found at necropsy examination.

The heart weighed 420 gm., being definitely hypertrophied; there was marked calcareous aortic stenosis. The heart muscle showed scattered fibrosis and an area of early, acute infarction along the obtuse border of the left ventricle.

The coronary arteries showed extensive atherosclerosis, with five complete old occlusions and widespread narrowing and calcification. A fresh occlusion from a ruptured atheromatous abscess was found in the distal portion of the left anterior descending coronary artery. There were extensive intercoronary anastomoses with mixing of colors in all parts of the coronary arterial tree and good injection distal to all points of occlusion.

Comment. This patient with spontaneous myxedema, extensive coronary artery disease, and aortic stenosis is presented because of the striking relation between the exacerbations of angina pectoris and thyroid medication. Thyroid was given in varying doses on several occasions. Many times it was associated with a marked increase in the severity and frequency of anginal pain.

Angina pectoris, which had been present for thirteen years prior to myxedema, is adequately explained by the severe coronary and valvular disease. The angina did not diminish significantly after the appearance of myxedema but the concomitant anemia is an additional factor which may well have prevented the expected improvement. It is also possible that progression of the coronary arteriosclerosis may have offset the protective effect of the hypometabolism. The hypometabolism may, indeed, have favored the long survival of this patient in the face of extensive coronary disease.[33]

The terminal episode of myocardial infarction occurred while the patient was still on thyroid medication but after the dose had been reduced for several days. The infarction may have been a consequence of the acute coronary occlusions. Ventricular tachycardia is a frequent terminating event in acute myocardial infarction and often appears as a result of myocardial irritability secondary to ischemia. On the other hand, it is possible that the ventricular tachycardia

was the initial event in the terminal illness; the myocardial infarction and acute occlusion may have resulted from reduced coronary blood flow and myocardial ischemia produced by the tachycardia.

DISCUSSION

Presence, Incidence and Significance of Coronary Occlusions and Narrowing: Their Relation to the Development of Collateral Circulation. In normal hearts showing no coronary arteriosclerotic narrowings or occlusions, intercoronary anastomoses larger than 40 micra are generally absent.[4] Fine communications, however, measuring less than 10 micra in diameter can be readily demonstrated in all hearts. Watery solutions injected into one coronary artery are always found in the other large coronary arteries. These fine communications are inadequate to protect the heart from the untoward effects of sudden coronary narrowing or occlusion. Clinical experience, pathologic findings[20,36] and experimental observations[37,38] clearly demonstrate that infarction usually results when an otherwise normal heart is subjected to sudden occlusion of a coronary artery by embolus, thrombus or subintimal hemorrhage, or in animals by ligation. It appears, therefore, that irrespective of the age of the individual, intercoronary anastomoses 40 micra or more in diameter usually do not exist in the absence of obstruction of these arteries or in the absence of other factors such as anemia, cardiac hypertrophy and valvular disease in which there is a relative insufficiency of blood supply.[4]

In contrast to the rarity of demonstrable, functionally significant anastomoses in normal hearts is the usual finding of anastomoses in hearts in which there were old, long-standing complete occlusions or extreme narrowing of the main coronary arteries and their branches. Large, grossly dissectible interarterial anastomoses were not seen in any normal hearts but they were present in 17 per cent of the hearts with old occlusions. There is, therefore, a great increase in intercoronary anastomoses, both in number and size, in hearts with coronary artery occlusions.[4]

The seeming inconsistency between the presence of long-standing obstructive arterial lesions and the absence of clinical or pathologic evidences of myocardial damage is dispelled by the demonstration of a rich collateral circulation in relation to the obstruction in each of these hearts. If coronary artery narrowing and occlusion proceed slowly, the obstruction to blood flow may be compensated by the opening of collateral channels. Although serious damage is usually avoided by the development of such collateral circulation, as has been demonstrated experimentally, the margin of safety, or as it may be termed "the coronary reserve," is reduced.

Pathogenesis of Angina Pectoris. The frequency with which coronary obstruction and myocardial fibrosis have been found in the hearts of patients with angina pectoris supports the concept that myocardial ischemia is present during attacks of angina pectoris.[39] The absence of fibrosis in some hearts with old coronary occlusion is evidence of the adequacy of the compensatory collateral circulation which developed in response to the occlusions. In these patients the occurrence of angina pectoris indicates that the coronary blood flow was not completely adequate at all times and suggests that the rate of flow or gradient of pressure through these collateral channels was diminished. The absence of fibrosis in some hearts from patients with angina pectoris indicates that angina is not necessarily associated with irreversible myocardial damage and that ischemic muscle may recover completely without anatomic lesions.

Additional support of the ischemic theory of angina pectoris is afforded by the temporary ischemic changes in T waves and S-T segments in electrocardiograms taken during such attacks;[40–42] by the induction of angina pectoris by effort, emotion and other states which increase the work of the heart; by the relief afforded by rest and other measures which lessen the work of the heart or increase coronary blood flow; and by precipitating attacks by breathing low concentrations of oxygen as well as by preventing attacks by the inhalation of oxygen.[43–45] Other factors which decrease coronary blood flow are lowered blood pressure such as is observed in shock from any cause; the low diastolic blood pressure in aortic insufficiency, and the decreased coronary flow in aortic stenosis; diminished cardiac output of tachycardia; and anoxia of the anemic (anemia), stagnant (congestive failure) or anoxic (cor pulmonale, etc.) types.

In cardiac hypertrophy the nutritional requirements of the myocardium are increased. The significance of the disproportion between

the amount of coronary flow and the hypertrophied muscle mass, even when the coronary arteries are normal, has been demonstrated by Wearn.[46] Gross[47] has shown that the capacity of the arterial tree is increased in cardiac hypertrophy, and Russow[48] and Fishberg[49] found that the total cross section of the primary coronary branches is enlarged in such hypertrophied hearts. A definite increase in interarterial anastomoses has been found by us in hypertrophied hearts.[4] If this anastomotic circulation is insufficient, local anoxia and pain may result. Several explanations[27–31] have been offered to account for angina pectoris in patients whose hearts show only mitral stenosis. In all of them the underlying mechanism is that of myocardial ischemia. Increased cardiac work or diminished coronary blood flow may similarly account for the appearance of angina pectoris in other forms of valvular disease.

Among conditions observed in this study which increase the work of the heart and, consequently, increase its nutritional requirements and produce angina pectoris the following may be noted: (1) effort and emotion, (2) infection, (3) arterial hypertension, (4) valvular stenosis and insufficiency, (5) anoxia caused by pulmonary disease or anemia, (6) tachycardia and (7) hyperthyroidism.

"Spasm" of the coronary arteries with diminished blood flow has also been invoked frequently to explain the precipitation of episodes of angina pectoris.[50] Attacks of angina brought on by exposure to cold or "by any disturbance of mind"[51] and prevented or terminated by nitroglycerin are difficult to explain solely on the basis of long-standing anatomic changes in the coronary arteries or myocardium. Spasm could result from a direct effect of adrenalin or other circulating substances on the smooth muscle of the arteries, or it could be induced by vasomotor reflex impulses. The vast accumulation of experimental observations of coronary vasoconstriction in animals cannot be transposed to man with assurance[52] but many recent observations in patients with angina pectoris now afford strong evidence of the existence and significance of vasomotor influences. Vasomotor reflex changes account for the effects on anginal attacks of atropine,[53,54] local chilling and anesthesia of the hands,[55] carotid sinus stimulation,[55] tobacco smoking,[56] pulmonary emboli[57] and gastrointestinal disorders.[58,59] Indeed, reflex coronary vasomotor spasm may be very important in increasing the mortality and the extent of myocardial necrosis following acute coronary artery occlusion.[60]

The existence of vasomotor effects which reduce coronary flow and of conditions which increase the myocardial requirements for blood is in no way incompatible with the demonstration of widespread pathologic changes in the hearts of patients with angina pectoris. The primary etiologic factors of coronary obstruction, valvular disease and arterial hypertension are not to be considered the exclusive cause of cardiac pain; rather they constitute the stage upon which various factors may operate. Thus coronary vasoconstriction, anemia, tachycardia, hypermetabolism or hypotension may act as precipitating agents in the production of pain in a patient whose coronary circulation is already compromised by arterial obstruction.

The underlying mechanism, then, of angina pectoris appears to be a relative disproportion between the requirements of the heart for blood and the supply furnished by the coronary arteries. This disproportion results in paroxysmal ischemia with its clinical counterpart, an attack of angina pectoris.

The effects of coronary artery disease upon the heart muscle and thereby upon clinical symptoms such as angina pectoris depend upon factors such as the location and rate of development of coronary obstruction, the speed of formation and functional adequacy of the collateral circulation, the rate and pressure gradient of coronary blood flow and the work requirements of the heart. It is because of the interplay of all these factors that one sees such marked variations in the extent of coronary disease in patients with angina pectoris irrespective of whether the angina is of short or long duration, whether or not myocardial infarction or congestive failure occurs or whether the patients die of cardiac or non-cardiac cause.

There are occasional statements in the literature suggesting that angina pectoris might occur in certain conditions among patients with normal hearts. These conditions include anemia,[61–63] coronary artery spasm,[62,64,65] thyrotoxicosis,[62] excessive exertion,[62,66] pulmonary arteritis[67] and gastrointestinal dysfunction.[68] It is conceivable that severe anemia can produce myocardial ischemia and hence cardiac pain. Angina pectoris has in fact been noted in children under the age of ten with hookworm anemia.[69] In none of these cases, however, was there the opportunity to establish the "normalcy" of the heart

through postmortem examination. One cannot rely on the youth of a patient[70] or a negative clinical study to establish the absence of heart disease. Rarely, however, a patient with angina pectoris comes to necropsy and a normal heart is found.[65] In such cases it is necessary to establish the absence of hypertension, for in one of our anginal patients with hypertension the heart weight was at the upper border of normal. Furthermore, one cannot be completely certain that the coronary arteries are normal unless they have been injected and carefully dissected.[71] In our study non-cardiac disease states did not produce angina pectoris unless there had already been a reduction of coronary reserve by preexisting coronary, valvular or hypertensive heart disease. Although there may be rare exceptions, we believe that a diagnosis of angina pectoris is tantamount to a diagnosis of organic heart disease.

Prognosis in Angina Pectoris. Mortality figures published by Eppinger and Levine,[72] Mackenzie[64] and White, Bland, and Miskall[34] show the average duration of life after the onset of angina pectoris to range from 4.5 years to ten years. In the large series reported by Parker, Dry, Willius and Gage[35] 50 per cent of the patients with angina pectoris were dead in eight years. In contrast, the average duration in our series is 4.1 years and the 50 per cent mortality rate is slightly more than two years. It is important to recognize that the patients in all these series, including our own, are specially selected. The series of Mackenzie, Eppinger and White are all based upon private cases, the majority having been seen on a consultation basis. To a large extent this is also true of Parker's series from the Mayo Clinic. Our own figures are derived from data on patients who died and were autopsied at a general hospital. Patients infrequently seek hospitalization for angina pectoris alone. Anginal patients may enter the hospital for congestive failure, acute infarction or for serious non-cardiac disease which either causes or in large measure contributes to their death. Forty per cent of the patients in our series succumbed to intercurrent non-cardiac causes. Emotional instability,[72,73] race,[62,74] heredity,[72] social status[62,75] and physical activity[62] are all factors which may influence prognosis. The differences among these series concerning the prognosis of angina pectoris may depend upon a sampling process in which many variable factors are operating.

In the present series hypertension, valvular disease and congestive failure were all found to have an adverse effect on survival in the patient with angina pectoris. A single episode of intercurrent myocardial infarction did not appear to influence survival in anginal patients. The contrary finding in other series may be based on differences in the series or the fact that terminal myocardial infarction was not excluded. Abnormal electrocardiograms have been found by others[34] to indicate a poorer prognosis. It has also been stated that in a patient with angina pectoris, the findings of a negative physical examination, a normal electrocardiogram and a normal heart x-ray are favorable prognostic signs.[76]

The physician seeing the patient with angina pectoris for the first time may use these observations as a guide in prognosis. His opinion will be further influenced by the number of years that the patient has had angina because the mortality is highest in the first two years. Finally, his judgment will be tempered by the knowledge that sudden death may supervene at any time.

SUMMARY

1. A clinico-pathologic study of angina pectoris was carried out in a group of 848 cases in which the coronary arteries were injected and dissected by the Schlesinger technic. The group consisted of 177 patients with angina pectoris of one month's duration or longer and 671 control patients without cardiac pain.

2. Not a single patient with angina pectoris in the entire series was found to be free of heart disease. All anginal patients had either coronary, valvular or hypertensive heart disease; 90 per cent of them had coronary narrowing or occlusion.

3. To clarify the relative importance of various types of heart disease in the production of angina pectoris, the incidence of angina among patients with a single form of heart disease was determined. Angina was found in 52 per cent of patients with coronary occlusion, in 16 per cent of those with valvular lesions, in 5 per cent of those with coronary narrowing and in 3 per cent of those with hypertension.

4. There was a clear positive correlation between the degree of coronary obstruction and the incidence of angina pectoris; among patients with occlusions of three main coronary arteries the incidence of angina pectoris was 85 per cent.

5. The serious prognostic import of angina pectoris in this series is evident from the mor-

tality figures. One-third of the patients were dead within one year after the onset of angina, half were dead within two years, three-quarters were dead within five years and nine-tenths within ten years. The average duration of angina pectoris differed according to the underlying etiology: it was shorter in valvular and longer in coronary heart disease.

6. Congestive failure was of more serious prognostic importance than angina pectoris in coronary disease and less serious in valvular disease.

7. An intercurrent episode of myocardial infarction did not shorten the prognosis of a patient with angina pectoris.

8. The underlying mechanism of angina pectoris appears to be a relative disproportion between the requirements of the heart for blood and the supply furnished by the coronary arteries; this disproportion results in paroxysmal relative ischemia. In coronary artery disease, angina pectoris, myocardial fibrosis and intercoronary anastomoses all result from myocardial ischemia; the first is a clinical expression, the second a pathologic end result and the third a compensatory response to ischemia.

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Seminars on Arteriosclerosis

Lipoproteins in Atherosclerosis*

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THE exact role of various lipids in the pathogenesis of atherosclerosis remains a controversial issue among investigators of this problem. This controversy centers about two issues, namely, whether lipid involvement in the lesion is primary or secondary to other changes in the vessel wall structure and which lipids (and from what source) are involved in production of lesions. It is essentially impossible at present to provide an unequivocal answer on the first issue. The evidence implicating primary non-lipid vascular alterations rests upon such features as (1) fibrotic or proliferative lesions in young individuals when it is stated that such lesions being devoid of lipid means that lipid involvement could not have been primary and (2) the known susceptibility of certain focal areas to develop atheroma earlier than other areas. The absence of lipid in a sclerotic lesion in a young individual may be due to the fact that there never was any present, but resorption of lipid that had been associated with the inception of the lesion could produce the same final result. The striking focal character of atherosclerosis should not be allowed to obscure the likelihood that a lipid metabolic disorder is involved in at least an equally significant degree.

Thus susceptible focal sites may be involved with atheroma only if the lipid metabolic error is present. These two facets of the problem are more likely complementary than mutually exclusive.

The major considerations in this discussion will be directed toward the second issue—which lipids are involved in lesion formation. The accumulated experimental and clinical evidence indicates that the lipids of serum are of importance in this disease, and hence a survey of the nature of serum lipid transport is necessary to an understanding of the relation of such lipids to atherosclerosis, in the clinical management of atherosclerosis when manifested by one of its serious sequelae, such as coronary artery disease.

Transport Vehicles for Lipids in Serum. Our ultracentrifugal investigations of the serum lipids of humans at all ages and of a variety of clinical categories as well as those of several animal species has led to at least some systematization in the concept of the nature of blood lipid transport. All the major lipids in blood, including glyceryl ester, cholesterol, cholesterol esters, phospholipids and fatty acids are transported in the form of giant lipoprotein molecules of several types. The spectrum of such lipoproteins present in a given human's blood or in that of an experimental animal is best described in terms of the individual lipoproteins demonstrable qualitatively and measurable quantitatively by the use of the ultracentrifuge. The basic technics and principles involved in ultracentrifugal flotation analysis of lipoproteins have been described in several previous publications.[1–5] From such ultracentrifugal studies has emerged the general picture that individual patients (or "normals") and animals show tremendous variations in the types and concentrations of lipoproteins present, but for a given individual at steady state (i.e., not being acutely manipulated by diet, drug or disease) there is a characteristic pattern of lipoproteins, stable over long periods, at least for portions of the lipoprotein spectrum. At least nine discrete lipoproteins have now been characterized in human blood. Broadly they may be separated and characterized as follows:

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The Low Density* group of Lipoproteins		The High Density Group of Lipoproteins
Species	Density (gm./cc.)	
S_f 2	1.050	Species of density = 1.12
S_f 4	1.040	Species of density = 1.07
S_f 6	1.035	
S_f 8	1.029	
S_f 10	1.023	
S_f 13	1.015	
S_f 17	0.99	
S_f 17–40,000	(<0.99)	

* The segregation on the basis of density of molecules is for convenience and for identification in the absence of more appropriate nomenclature. Within the low density group the molecules are named by their characteristic flotation rates under specified ultracentrifugal conditions. Units are S_f units (Svedbergs of flotation). 1S_f unit = migration rate of 10^{-13} cm./sec./dyne/gm. at 26°C. in a medium of NaCl solution of density 1.063.

In the low density group of lipoproteins up through S_f 17 we have discrete components. Between S_f 17 and S_f 40,000 is a series of components so closely spaced that it is not possible to resolve discrete, homogeneous components, although the various components within this range may exist as such. The upper limit of S_f 40,000 represents the rate of the lipoproteins known commonly as chylomicrons. Attention in this discussion will be given almost exclusively to the low density group of lipoproteins, the high density lipoproteins to be treated elsewhere.[6]

The simplest pattern observed is that seen in the normal experimental animal and in the majority of children and adults below twenty-five years of age. This is the pattern showing no appreciable concentration of any lipoproteins above a certain limit (S_f 8 or 10 for the rabbit, S_f 6 for the human). Deviating from this simple pattern there is a regular sequence of types of patterns which may be regarded by itself as a progression of a lipid metabolic defect reflecting itself in the lipid transport mechanism. The nature of this progression is illustrated in Table I.

While the general progression shown in Table I gives the broad classification of patterns, it does not specify the exact concentration one species must reach before the successive ones appear. It does specify, however, that S_f 17 molecules will not be at appreciable concentration unless S_f 13, S_f 10 and S_f 8 are also present at moderate or high concentration. Further, the S_f 17 may be two times as concentrated in one serum as S_f 13 while the reverse may obtain in the serum of another individual. For a given individual the relative concentrations remain closely similar for periods at least as great as one year. In fact all the molecules below S_f 20 are reasonably stable in concentration in a single individual for periods of months and are certainly not acutely influenced by meals (see later section on biologic variation).

TABLE I

LIPOPROTEIN TRANSPORT AS A MEASURE OF LIPID METABOLIC DEFECT

(HUMAN)

"*Normal*" Pattern

(1) Lipoproteins of S_f 4 and/or S_f 6 present at low or moderate concentrations. *Minimal* levels of higher S_f components except for transient elevations in S_f 30–40,000 following fatty meals.

"*Minimal*" Defect

(2) Lipoproteins of S_f 4 and/or S_f 6 at increased concentrations but without any increase in higher S_f components as compared with (1).

"*Minor*" Defect

(3) Lipoproteins of S_f 4 and/or S_f 6 *plus* S_f 8 in increasing concentration.

Progressively "*More Severe*" Defect

(4) $S_f4 + S_f6 + S_f8 + S_f10$

(5) $S_f4 + S_f6 + S_f8 + S_f10 + S_f13$

(6) $S_f4 + S_f6 + S_f8 + S_f10 + S_f13 + S_f17$

(7) $S_f4 + S_f6 + S_f8 + S_f10 + S_f13 + S_f17 + S_f17–20$

(8) $S_f4 + S_f6 + S_f8 + S_f10 + S_f13 + S_f17 + S_f17–20 + S_f20–40$

(9) $S_f4 + S_f6 + S_f8 + S_f10 + S_f13 + S_f17 + S_f17–20 + S_f20–40 + S_f40–40,000$
(In this group the S_f 40–40,000 can be of transient existence following meals or may be sustained even post-absorptively.)

(10) "*Most Severe*" Defect
As in (9) except that the S_f 4 and S_f 6 may be depressed to quite low concentrations. (This may be regarded as a general *shift* toward higher S_f lipoproteins, and is comparable to that which appears in the rabbits in the later phases of cholesterol–Wesson oil feeding.)

Chemical Structure of the Serum Lipoproteins. Lindgren and Nichols[7] have developed technics for the isolation of the individual lipoproteins, free essentially of those of higher and lower S_f classes. These isolated species may then be subjected to chemical analysis for internal structure. Such studies have revealed large differences between the various lipoproteins in structure to add to the already known differences in physicochemical properties. The major features of composition are demonstrated in Table II.

From Table II it is seen that the actual lipid

constituents which are transported via the different lipoproteins are quantitatively and qualitatively different. The major neutral fat (glyceryl ester) bearing molecules are those of S_f 17 and higher whereas in general the major cholesterol-bearing molecules are those of S_f 17 and lower. Thus since enormous variations in the relative concentrations of the individual lipoproteins exist from one person to another, it should be evident that a determination of the total lipid level by the usual classic chemical technics will fall far short of an adequate description of the true manner in which the lipids are being transported.

TABLE II

CHEMICAL CONSTITUENT	S_f 4	S_f 6	S_f 8	S_f 10	S_f 13	S_f 17	S_f 17–40	S_f 40–40,000
Total cholesterol	~30%	Decreasing steadily						5%
Fraction of cholesterol esterified	~75%	Decreasing steadily						0%
Phospholipid	~25%	Decreasing steadily						~5%
Protein	~25%	Decreasing steadily						5%
Glyceryl ester	← Absent or very low % in this range →						Increasing steadily	75–85%

Probable Metabolic Significance of Elevated Levels of Certain Lipoproteins. The question arises immediately once we know that individuals do differ in the extent of lipid transport error—why are they different and what role do these molecules play in over-all metabolism? Several lines of evidence which we have been able to develop point quite definitely to the view that all the molecules from S_f 40,000 down to S_f 4 (and possibly into the high density class) represent a sequence of molecules in a metabolic chain involved in the ultimate utilization of glyceryl esters and/or fatty acids. In a sense the cholesterol, phospholipids and protein may be part of a prosthetic fragment.

The evidence that the components of high S_f value are progressively transformed into those of the lower S_f classes is the following:

Graham et al.[8] have shown that the administration of heparin to rabbits and humans produces a reaction that causes rapid conversion of molecules above 30 S_f units to those below 30 S_f units. Then slower reactions convert these molecules to those of successively lower S_f classes.

Pierce[9] has shown that the cross injection of molecules above 50 S_f units from one rabbit to another results in a stepwise conversion of these transfused molecules to successively lower S_f categories followed with ultimate clearance from the blood, presumably by the normal course of fat metabolism.

The administration of high fat meals in normal humans results in a transient elevation of molecular classes above 60 S_f units. Then there is a stepwise conversion of such species to those of progressively lower S_f classes. It has been possible ultracentrifugally to follow this lipemic load down to S_f 30, with the lower S_f species in this range increasing at the same time the higher S_f species are decreasing in concentration.

From tracer studies now in progress[10] it appears that the average lifetime of all the lipoprotein species of the low density group is of the order of several hours. Therefore, the most probable explanation of a given concentration of a particular lipoprotein is that it is this steady state concentration at which the influx and utilization rates are equal. If the influx rate is increased ("loading"), the steady state concentration will build up to a level such that the utilization rate becomes equal to the influx rate. On the other hand, if utilization rate is depressed by some blocking mechanism, the steady state concentration will build up until the utilization rate again equals the influx rate. One evident fact is that while large fluctuations may be seen in the lipid transport load down to S_f 30 following acute fat ingestion, no detectable changes occur in the steady state levels of the serum lipoproteins from S_f 30 to S_f 4. If these latter groups are directly concerned in the metabolism of ingested fat, they must be equilibrated with a very much larger pool of lipids than is the case for the higher S_f molecules or the utilization rate of molecules below S_f 30 may increase suffi-

ciently in response to small increments in load so that the habitual steady state level is maintained. It is only with a single dose of heparin that the pouring of large quantities of substances from the S_f 30–100+ classes into those between S_f 20 and 30 is rapid enough such that the utilization system below 30 S_f units is overloaded, with a resultant rise in steady state concentration, which lasts for a period up to several hours during which time this load is progressively transformed to still lower S_f classes.

Relationship of Lipoproteins to Vascular Disease, Particularly Atherosclerosis. Earlier in this article it was pointed out that the evidence is strong that blood lipids are in some way associated with atheromatous vascular disease. Given the knowledge that the blood lipids (including cholesterol, its esters, phospholipids and fats) circulate in the form of a series of types of lipoproteins, the question arises—are all, any or certain special ones of the lipoproteins related to atherosclerosis? Can one attach *differential* significance to some lipoproteins with respect to vascular disease? To answer this question requires a comparison of the lipoprotein findings in individuals with developing atherosclerosis with those individuals who do not have the disease. Unfortunately in the human this is beset with difficulties. In the ostensible "normal," with a negative history, physical examination, cardiogram and x-ray, we must recognize that there will still be a large number of individuals with appreciable atherosclerosis. This occurs because unless there has been a clinical sequel, atherosclerosis is an undetectable, silent disease. On the other side, it is difficult to find a group of humans with definite atherosclerosis and to quantitate its extent. Even if we know that atherosclerosis is present, what we really would like to know is its rate of development rather than its quantitative extent in the form of new plus old disease. The entire problem is more readily solvable in the experimental animal when we can autopsy at intervals sufficient numbers to determine rate of progression of the disease. As the best approximation in the human we have elected to study patients with myocardial infarction as compared with presumably normal individuals. Using such groups we believe it is justifiable to say that atherosclerosis, at least of the coronary arteries, will on the average, be more extensive in quantity and rate of progression in the infarct patients than in the normals although we must be fully aware that there will be overlapping between the groups. In essence this will mean that certain of the so-called normals will have more atherosclerosis established and more developing than certain of the myocardial infarction patients, but that this will not be the case in a statistical group sense.

In the experimental rabbit the summary of the observations of our group have indicated that there is unquestionably differential significance to the various lipoproteins which appear in the serum under a variety of experimental conditions. Several experimental states have been studied: (1) Rabbits fed cholesterol, (2) rabbits fed cholesterol + Wesson oil; (3) rabbits fed cholesterol + Wesson oil + potassium iodide and (4) alloxanized rabbits fed cholesterol.

For the rabbit in all these types of experiments there is no positive correlation, and even possibly a negative one ($r \cong -0.32$) between the serum levels of lipoproteins of S_f 10 and less which are present during the active phase of atherosclerogenesis. Thus severe atherosclerosis often develops with low levels of this class of lipoproteins (Fig. 1) whereas no atherosclerosis develops in spite of ten to fifteenfold increases in the concentration of such lipoproteins over their normal levels. However, there is a very high correlation ($r = 0.8$) between the concentration of lipoproteins of the S_f 10–30 class which develops and the degree of atherosclerosis measured at autopsy in all these types of experiments quoted previously. In certain groups of animals there is also a good correlation between degree of atherosclerosis and the total blood cholesterol. However, this is only because of the fact that in these particular animals the S_f 10–30 molecules account for a high proportion of the total cholesterol. That the total blood cholesterol itself is not the important feature has been nicely demonstrated by Pierce[11] in our laboratory studying the Duff[12] type of alloxanized rabbit. Duff has previously shown that feeding cholesterol to alloxan diabetic rabbits results in great elevations of serum cholesterol, to levels over 2,000 mg. per cent (Pierce actually has some with 5,000 to 10,000 mg. per cent), with minimal or no atherosclerosis developing. Pierce has shown that in such rabbits the cholesterol is transported in the form of molecules, primarily of the S_f 40–100 and higher classes, rather than in the S_f 10–30 class, as in the case of straight cholesterol feeding experiments. It appears, therefore, that high concentrations of molecules above S_f 50, with concomitant huge elevations

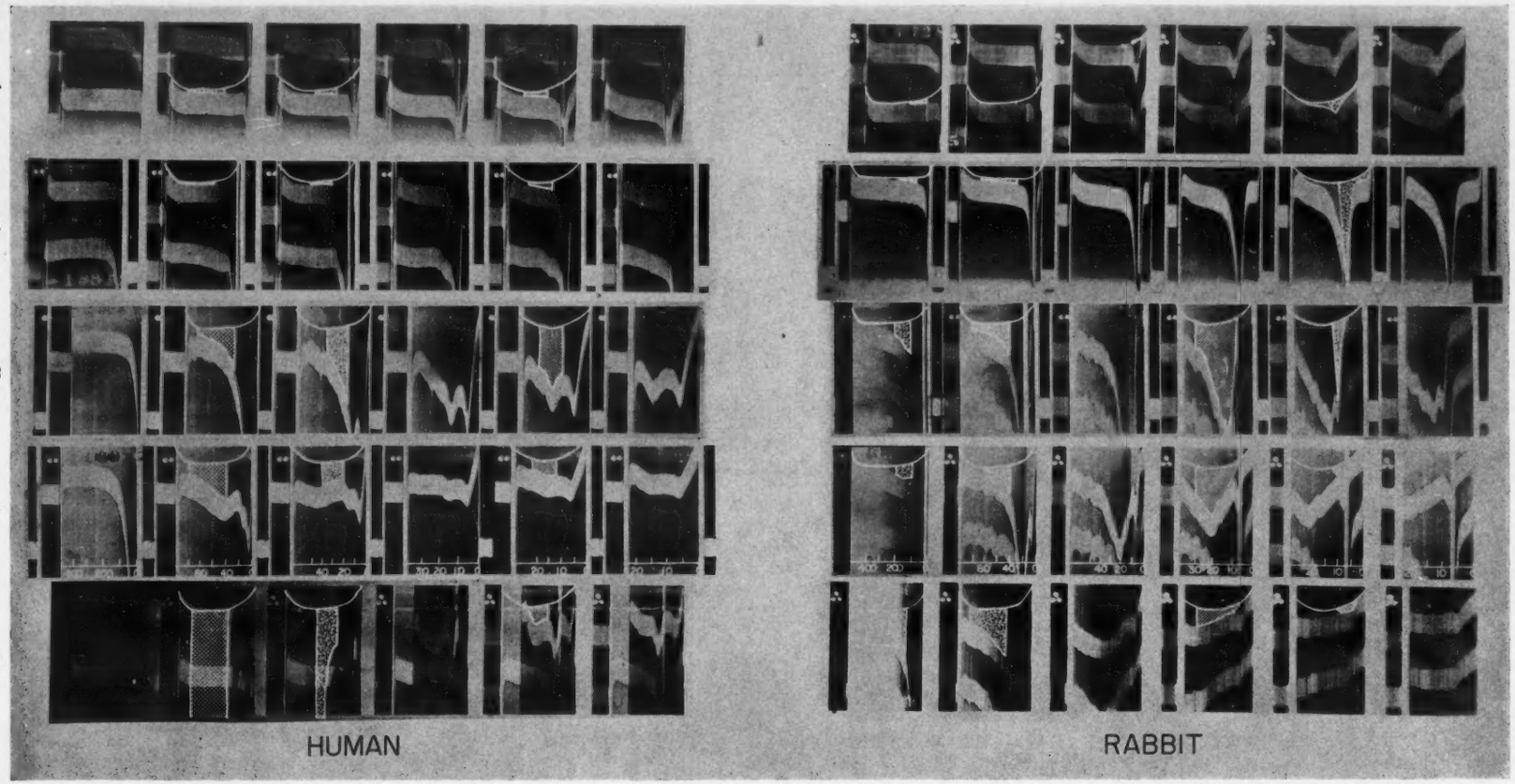


FIG. 1. Ultracentrifugal flotation patterns showing the increase in the lipid metabolic defect in the human and the experimental rabbit. In all these figures the S_f rates can be read off the S_f scale placed on all frames and concentrations of various lipoprotein fractions are proportional to the shaded areas. A, shows the flotation pattern of a normal child and a normal rabbit, both having low concentrations of lipoproteins below S_f 10 and trivial concentrations above S_f 10. B, shows the patterns for a normal human and for a rabbit with elevation of the concentrations of lipoproteins below S_f 10 but without appreciable elevations of lipoproteins of higher S_f classes. C, shows corresponding patterns for human and rabbit with moderate concentrations of lipoproteins of S_f 10 and less, but with great elevations in the S_f 12–20 and 20–40 class in the human and S_f 10–30 class in the rabbit. This rabbit developed marked atherosclerosis. D, shows analogous patterns for human and rabbit with marked elevation of S_f 12–20 class in human and S_f 10–30 class in rabbit, but with depression of the concentration of lipoproteins of S_f 10 and less. This rabbit also developed marked atherosclerosis. E, shows the manifestation of severe lipid metabolic error in human and rabbit. Note the low concentration of lipoproteins below S_f 10, moderate concentration of lipoproteins of S_f 12–20 class in the human and S_f 10–30 class in the rabbit, and big concentration of lipoproteins from S_f 20–100 in both human and rabbit.

of serum cholesterol, do not lead to atherosclerosis. In fact, in these experiments with alloxanized animals Pierce finds an inverse relationship of total cholesterol with degree of atherosclerosis since, when the cholesterol is very highly elevated, it is primarily in molecules > 50 S_f units which are apparently non-atherogenic and are not strongly associated with those lipoproteins that are atherogenic. It is an excellent illustration of the incorrect conclusion one is led to by the use of total serum cholesterol as a general index of atherosclerogenesis. At the same time these studies provide supplementary evidence of the differential significance of the various lipoproteins for atheroma formation. Throughout all types of rabbit experiments we have done, one common feature is evident, that is, elevations of the S_f 10–30 class of lipoproteins accompanies atherosclerosis. Total blood cholesterol correlates with atherosclerosis only in those particular types of experiments in which cholesterol elevation is associated with elevation of the S_f 10–30 class of lipoproteins.

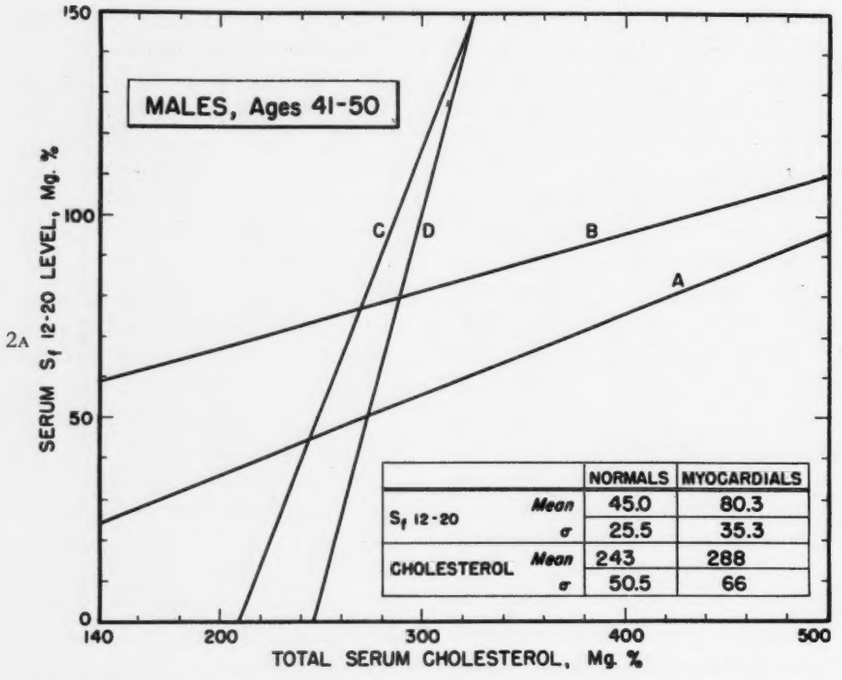
In testing for differential significance of certain lipoproteins in human atherosclerosis we have studied the correlations between serum levels of various lipoproteins and atherosclerosis, using normals vs. myocardial infarctions as test groups. The evidence presented later shows that one region of the lipoprotein "spectrum," between S_f 10 and S_f 20 shows a high correlation, but that this correlation is less for the lipoprotein classes immediately on either side of these limits. Actually within the region of S_f 10–20 the correlation appears best if the S_f 10 molecule itself is not included. Hence we may refer to the region as the S_f 10–20 class, with S_f 10 itself excluded or to the S_f 12–20 region. It can be further shown that the correlation between the S_f 12–20 lipoproteins and atherosclerosis is much better than for total serum cholesterol and that the S_f 12–20 lipoproteins correlate well with atherosclerosis even when we compare the infarct patients with normals who show the same serum cholesterol, patient for patient.

This study and our previous reports are based upon critical comparison of two human groups: (1) individuals that have had a myocardial infarction and (2) individuals that are presumably normal in that they evidence no clinical sign of atherosclerosis and are in active physical condition normal to their mode of living. Although other manifestations of disease with atherosclerotic complications are discussed, particular use is made of patients that have survived a myocardial infarction; for coronary artery disease of this type can be diagnosed with a high degree of reliability if patients are screened on a basis of objective criteria of electrocardiographic changes plus subjective signs plus a sequence of temperature elevation, leukocytosis or increased sedimentation rate.[1] This criterion group probably is manifesting a complication of atherosclerosis of the coronary arteries in an estimated 90 to 95 per cent of cases. Among normals, atherosclerosis is consistently reported with high occurrence rate from autopsy reports.[13] Presumably for many years of evolution of the atherosclerotic state no external sign of the disease may be manifest. It is estimated that in any group of adult males that 30 to 50 per cent of supposed normals may be actively developing arterial atheroma.[14] Thus the statistical comparisons that are made between presumed normals and atherosclerotics are of limited quantitative interpretation in crude form in that a population of approximately 95 per cent atherosclerotics is contrasted with a population of 50 to 70 per cent "true normals" admixed with 50 to 30 per cent of atherosclerogenic normals. However, it is possible to estimate correction of this comparison for the impurity of the latter criterion group as will be described in a later section.

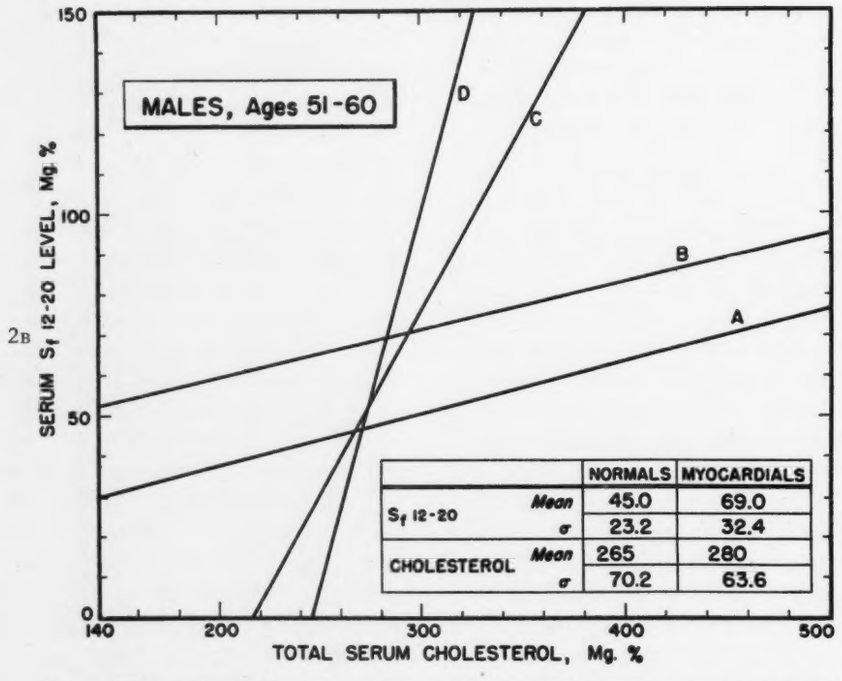
Between the ages of forty-one to fifty years we have studied 273 normal males and sixty-four males surviving myocardial infarction; similarly between fifty-one to sixty years of age the groups are 126 normals and ninety-two males with myocardial infarction. Several types of approach to the analysis of the data may be made in the effort to determine the relationship of S_f 12–20 lipoprotein and of total serum cholesterol measurements to atherosclerosis. Both over-all relationships and relationship of each measure independent of the other were studied. Toward this end the technics of matched groups and biserial correlations were used. Inasmuch as both methods yielded the same relative conclusions in different form, both are being presented.

MATCHED SERIES METHOD

The mean values for S_f 12–20 lipoproteins and total cholesterol for all groups studied and the corresponding regression plots (showing the relationship of S_f 12–20 and cholesterol both in



2A



2B

FIG. 2. The regression lines for normals and myocardial infarctions for cholesterol values and S_f 12–20 values from a study of both determinations on the same serum sample from each individual considered. These lines are calculated from the correlation coefficients between serum cholesterol and S_f 12–20 levels, the means and the standard deviations of both measurements. These values are indicated in the figure. Averaging data on scatter diagrams by columns in either direction indicate rectilinear regression. From these lines the mean S_f 12–20 level can be read for normals or infarcts at any cholesterol level, and conversely the cholesterol level for normals or infarcts can be read for any S_f 12–20 level. Lines A and B show the mean S_f 12–20 level at any cholesterol level in normals and myocardial infarcts, respectively. Lines C and D show the mean cholesterol levels at any S_f 12–20 level in normals and myocardial infarcts, respectively. A, is calculated from the data for 41–50 year old males (273 normals and 64 myocardial infarctions). B, is calculated from the data for 51–60 year old males (127 normals and 92 myocardial infarctions).

normals and myocardial infarcts) are given in Figure 2. The regression lines show for the two populations the mean S_f 12–20 at any serum cholesterol level and the mean cholesterol level at any serum S_f 12–20 level. Thus it is seen from the regression plots that the S_f 12–20 lipoprotein level is approximately 25 mg. per cent higher in myocardial infarcts than in normals at any serum cholesterol level throughout the entire cholesterol range. Conversely for any S_f 12–20 level, the myocardial infarcts show higher serum cholesterols than normals over part of the range and show lower serum cholesterol levels than normals over part of the range (above 50 mg. S_f 12–20 in the fifty-one to sixty year age group). A quantitative interpretation (together with an estimate of errors) of the relationships implicit in the regression data can be visualized by the preparation of matched series of cases of myocardial infarction vs. normals. Matched series have been used to assess the relationship of S_f 12–20 lipoproteins to atherosclerosis, while nullifying the effect of serum cholesterol *per se*, and conversely to assess the relationship of serum cholesterol to atherosclerosis, while nullifying the effect of S_f 12–20 lipoproteins. Thus the cases of myocardial infarction were listed by cholesterol levels. From the normal data cases were matched at random at corresponding cholesterol levels. Then the S_f 12–20 levels for the myocardial infarctions were compared with those for the normals that have been matched with these infarcts at the same age and serum cholesterol. Similarly the infarct cases were listed by S_f 12–20 levels and matched at random with normals having the same S_f 12–20 levels. Then the serum cholesterol levels were compared for the two groups. The data obtained in this way are presented. (Table III.)

The data in Table III may be interpreted as follows: (A) for the forty-one to fifty year age group, at the same serum cholesterol, the myocardial infarctions average 20.1 mg. per cent higher in S_f 12–20 levels than normals. At the same S_f 12–20 levels the myocardial infarctions average 19.1 mg. per cent higher in serum cholesterol than do normals. These differences are both significant in the forty-one to fifty year age group, the S_f 12–20 difference being 0.5 standard deviations of the mean difference and the cholesterol difference being 0.4 standard deviations of the mean difference, both mean differences being for the matched series. (B) For the fifty-one to sixty year age group at the same serum cholesterol the myocardial infarctions average 13.4 mg. per cent higher in S_f 12–20 levels than do the normals. At the same S_f 12–20 levels the myocardial infarctions do not show a significantly higher serum cholesterol level than do the normals. The difference in S_f 12–20 level is significant between infarcts and normals and is 0.46 standard deviations of the mean difference.

Thus for both age groups there is a segregation of infarcts from normals by S_f 12–20 measurements, independent of the serum cholesterol. However, while the forty-one to fifty year age group is segregated approximately as well by serum cholesterol measurement, independent of S_f 12–20, the fifty-one to sixty year age group infarcts are not significantly segregated by serum cholesterol measurements.

Unfortunately in this matching procedure thirty-two cases of infarction with S_f 12–20 levels above 70 mg. per cent could not be matched by normals. This has minimized the ability of the S_f 12–20 measurement to segregate infarcts from normals. A closer approximation to the over-all relationships of both measurements may be obtained for all the 156 cases of myocardial infarctions from forty-one to sixty years of age using the appropriate regression lines to match the cases. These data are given in Table IV and Figure 2.

Thus it is seen that making use of the entire 156 cases the S_f 12–20 measurement significantly segregates myocardial infarcts from normals, independent of the serum cholesterol levels. However, for the same group, serum cholesterol does not significantly segregate myocardial infarctions from normals, independently of the S_f 12–20 levels.

Hypercholesteremia (levels over 300 mg. per cent) has long been considered to be associated with atherosclerosis. However, there is reason to believe that there are differences in atherosclerotic activity even among the hypercholesteremics. To study this question we have compared (for serum cholesterols over 300 mg. per cent) all the normals (134 cases) with all the myocardial infarctions (ninety cases) of corresponding age and sex. A slight adjustment between the two groups, correcting to the same serum cholesterol level, was made using the regression equation. (Actual serum cholesterol mean for coronaries = 355; for normals = 347.) When infarcts are compared with normals, both at the same mean cholesterol (355 mg. per cent), the S_f 12–20 level in the myocardial infarcts is

TABLE III

MYOCARDIAL INFARCTS MATCHED WITH NORMALS BY SERUM CHOLESTEROL LEVELS OR BY S_f 12–20 LIPOPROTEINS*

I. Matched by Serum Cholesterol

(A) 41–50 yr. age group

	No. of Cases	Mean Serum Cholesterol	Mean S_f 12–20 Level
Myocardial infarcts	55	291.3 mg. %	73.8 mg. %
Normals	55	291.5 mg. %	53.7 mg. %
		Difference in S_f 12–20 = 20.1 ± 5.5† (Significant $p < 1\%$)	

(B) 51–60 yr. age group

	No. of Cases	Mean Serum Cholesterol	Mean S_f 12–20 Level
Myocardial infarcts	69	276 mg. %	62.4 mg. %
Normals	69	276 mg. %	49.0 mg. %
		Difference in S_f 12–20 = 13.4 ± 3.5 (Significant $p < 1\%$)	

II. Matched by S_f 12–20 Levels

(A) 41–50 yr. age group

	No. of Cases	Mean Serum Cholesterol	Mean S_f 12–20 Level
Myocardial infarcts	55	292.3 mg. %	74.3
Normals	55	273.2 mg. %	74.3
		Difference in cholesterol = 19.1 mg. % ± 6.4 (Significant $p < 1\%$)	

(B) 51–60 yr. age group

	No. of Cases	Mean Serum Cholesterol	Mean S_f 12–20 Level
Myocardial infarcts	69	283.3 mg. %	60.4
Normals	69	276.3 mg. %	60.4
		Difference in cholesterol = 7.0 ± 8.1 (not significant)	

* Lipoprotein and cholesterol determinations were done on aliquots of the same serum sample from each individual in the study.

† The error estimated is the standard error of the difference of the means appropriately calculated for a matched series, with the correction for intercorrelation.

89.5 mg. per cent while that of the normal group is 64.5 mg. per cent. The difference of 25 mg. per cent is highly significant ($p << 1$ per cent).

If the data for the normals are corrected by the regression equation so that the S_f 12–20 levels are equal, in the myocardial infarcts and normals, the mean cholesterol is not higher in the infarcts than in the normals.

TABLE IV

ALL MYOCARDIAL INFARCTIONS FROM 41–60 YEARS MATCHED BY AGE AND BY S_f 12–20 OR CHOLESTEROL FROM THE REGRESSION EQUATIONS

(A)	Matched at the same cholesterol levels:	
	(for 156 cases)	S_f 12–20 levels average 23.1 mg. % higher in myocardial infarcts than in normals.
(B)	Matched at the same S_f 12–20 levels:	
	(for 156 cases)	Serum cholesterol averages 1.1 mg. % less in myocardial infarcts than in normals.

A special group of interest, because of its exceptionally high atherosclerotic activity, is that manifesting the syndrome, xanthoma tuberosum. These patients are quite uniformly hypercholesteremic but appear to have manifestations of atherosclerosis in excess of what might be anticipated for their degree of hypercholesteremia. A matching of twelve cases of xanthoma tuberosum with hypercholesteremic normals was done.

The twelve cases of xanthoma ranged from 275 mg. to 640 mg. per cent serum cholesterol, averaging 489 mg. per cent. The S_f 12–20 lipoproteins in these cases ranged from 76 mg. per cent to 520 mg. per cent, averaging 250 mg. per cent. The closest matched group of hypercholesteremic normals that was possible showed a range of 423 to 492 mg. per cent serum cholesterol, averaging 447 mg. per cent. The S_f 12–20 lipoproteins ranged from 48 mg. per cent to 99 mg. per cent, except for one case at 300 mg. per cent, and averaged 85 mg. per cent. A slight correction of the normal group to identical serum cholesterol level as for the xanthomas was made by use of the regression equation. Thus the equivalent normals at 489 mg. per cent serum cholesterol would have an S_f 12–20 level of 96 mg. per cent. Thus the extraordinary atherosclerotic tendency of xanthoma tuberosum is explainable on the basis of their level of S_f 12–20 lipoproteins being about two to one-half times as high as even equivalently hypercholesteremic normals.

In summary it appears from all the matching analyses that the S_f 12–20 lipoprotein measurement shows a consistent difference between myocardial infarcts and normals, independent of the serum cholesterol, whereas the serum cholesterol measurement shows a difference between infarcts and normals only within the forty-one to fifty year age group, independent of S_f 12–20 levels.

The separate study of all hypercholesteremic myocardial infarcts and normals shows an elevation of S_f 12–20 lipoproteins in infarcts over that of hypercholesteremic normals, independent of the serum cholesterol itself.

BISERIAL CORRELATIONS

It would be useful to be able to estimate the quantitative relationships between either serum cholesterol or S_f 12–20 lipoproteins and degree of atherosclerotic activity in the human. The only quantitative segregation provided on a scale of atherosclerotic tendency in these data is apparent normal health or presence of myocardial infarction. We have used the technic of biserial correlation coefficients to make some estimate of the degree of association of our two measurements with degree of atherosclerotic activity, comparing the "normal" population with the population of myocardial infarctions. It is quite possible that the required conditions for use of the biserial r are not met and we have not proven to have met them in this situation, for it would require that the degree of atherosclerotic activity be continuously and normally distributed for the combined population sample being used. The skewness of the S_f 12–20 and cholesterol distributions for over-all populations was corrected for by normalization of the scale of these values. These correlation coefficients may or may not be usable in calculating true coefficients of determination. However, they may be used as a basis for estimating the relative importance of total serum cholesterol and the various serum lipoproteins in association with atherosclerosis as both measurements were made on identical samples of sera. Biserial r's and Pearson r's are given for appropriate age groups in Table v for these intercorrelative measures for 156 myocardial infarctions and 400 normal males between forty-one and sixty years of age. By splitting the group as the forty-one to fifty and fifty-one to sixty year old groups, the relationship of increasing cholesterol with age is minimized and infarctions are compared to normals of nearly equivalent age.

It is a difficult problem to account for all

the significant factors that distinguish a population of myocardial infarcts from true normals and the fraction of this accountability that can be associated with serum S_f 12–20 lipoproteins or serum cholesterol. In the forty-one to fifty age group crude analysis shows that S_f 12–20 and

TABLE V

A. *Biserial coefficients of correlation of serum cholesterol with degree of atherosclerosis, bi r (chol. vs. athero.), and serum S_f 12–20 levels with degree of atherosclerosis, bi r (S_f 12–20 vs. athero.).*

41–50 yr. old males	273 normals	average age = 45 yr.
	64 surviving myocardial infarctions	average age = 45 yr.
bi r (chol. vs. athero.) =	0.46 ± 0.07	(normalized distribution of cholesterol)
bi r (S_f 12–20 vs. athero.) =	0.62 ± 0.06	(normalized distribution of S_f 12–20)
51–60 yr. old males	127 normals	average age = 55.0 yr.
	92 surviving myocardial infarctions	average age = 55.3 yr.
bi r (chol. vs. athero.) =	0.30 ± 0.12	(normalized distribution of cholesterol)
bi r (S_f 12–20 vs. athero.) =	0.61 ± 0.06	(normalized distribution of S_f 12–20)

B. *Pearson coefficients of correlation between serum S_f 12–20 and total serum cholesterols*

273, 41–50 yr. male, normals	r(chol. vs. S_f 12–20) = 0.40 ± 0.055
64, 41–50 yr. male, surviving myocardial infarctions	r(chol. vs. S_f 12–20) = 0.28 ± 0.13
337, 41–50 yr. male, normals and infarcts	r(chol. vs. S_f 12–20) = 0.49 ± 0.04
127, 51–60 yr. male, normals	r(chol. vs. S_f 12–20) = 0.39 ± 0.08
92, 51–60 yr. male, surviving myocardial infarctions	r(chol. vs. S_f 12–20) = 0.31 ± 0.10
219, 51–60 yr. male, normals and infarcts	r(chol. vs. S_f 12–20) = 0.51 ± 0.05

C. *Reliability Measurements*

Serum S_f 12–20 coefficient of reliability r (S_f 12–20 vs. S_f 12–20) for one determination correlated with a second sample analysis over a year's time corresponding to the collection of the data (includes biologic and technical errors).

$$r(S_f\ 12\text{–}20 \times S_f\ 12\text{–}20) = 0.67 \pm 0.05 \text{ for } 117 \text{ observations}$$

Serum cholesterol coefficient of reliability r (chol. vs. chol.) for one determination correlated with a second sample analysis over a year's time corresponding to the collection of the data (includes biologic and technical errors).

$$r(\text{chol.} \times \text{chol.}) = 0.75 \pm 0.07 \text{ for } 45 \text{ observations}$$

Redetermination on the same serum sample

$r'(S_f\ 12\text{–}20 \times S_f\ 12\text{–}20)$	= 0.80* ± .04	80 cases
r′(chol. × chol.)	= 0.90 ± .001	532 cases

* This value is characteristic for the period of the collection of these data. Current technical reliability measurements indicate redetermination of the same samples, $r'(S_f\ 12\text{–}20 \times S_f\ 12\text{–}20) = 0.90\text{–}0.95$.

cholesterol account for approximately 38 per cent and 25 per cent, respectively; in the fifty-one to sixty age group S_f 12–20 accounts for approximately 37 per cent and cholesterol accounts for 9 per cent, if we were able to say that degree of atherosclerosis is continuously and normally distributed in the studied sample of normal and atherosclerotic males. Other corrective factors must be taken into account to measure 100 per cent of the factors involved in segregating myocardial infarction-atherosclerotics from normals. They are as follows:

Accumulated Atherosclerosis vs. Atherosclerotic Activity. Measurement of derangement of lipid metabolism by S_f 12–20 lipoprotein molecules is thought to indicate active atherosclerogenesis. Are myocardial infarctions caused by active or accumulated atherosclerosis? If they are primarily disturbances of accumulated atheroma, then myocardial infarction is not a pure criterion of active atherosclerosis and is of value only through the relationship of degree of atherosclerosis vs. rate of accumulation of atherosclerosis. This error has not been estimated and cannot be estimated at this time.

Impurity of the "Normal" Population. The normal population is composed of a group of true normals whose atherosclerotic activity is insufficient to produce significant atherosclerosis, and normals whose atherosclerosis has not yet advanced to clinically detectable levels or to manifest complications of atherosclerosis. It is variously estimated that 30 to 50 per cent of normals are moderately to severely atherosclerotic. We have attempted to estimate from S_f 12–20 values in the normal population the number of true normals. This estimation is based upon the observation that the distribution of S_f 12–20 levels in the normal population is markedly skewed in the region of the distribution observed for the myocardial infarction population. If this skewing is a measure of the number of atherosclerotics among the normals, the true normals are 67 per cent of the group and the mean and standard deviation of the true normals is 34 mg. per cent and 18 mg. per cent contrasted to 70 mg. per cent and 30 mg. per cent for myocardial infarctions and 45 mg. per cent and 24 mg. per cent for the unsegregated normals.

Focal Factors in Atherosclerosis. The focal character of atherosclerosis, especially when of mild degree, is indisputable, but this is consistent with the role of lipids in its pathogenesis. It is entirely reasonable that given the necessary lipid metabolic abnormality, certain susceptible sites will be earlier and more extensively involved. It may well be the case that if such lipid metabolic abnormality is not present, even susceptible focal sites will not show appreciable disease. In this factor alone there can be great individual variation even though we believe it is justifiable to say that atherosclerosis of the coronary arteries (and its rate of development) will on the average be more pronounced in patients with myocardial infarction than in normals. The exact degree to which this factor prevents accounting for the total variance between atherosclerotics and normals cannot be estimated at this time. This factor is of importance and it is hoped that follow-up autopsy will enable an assessment of its magnitude.

Reliability, Errors and Consistency of Measurements. Any measured relationships between such factors as total serum cholesterol or S_f 12–20 lipoproteins with atherosclerosis are influenced by errors of measurement and biologic variation with time. Such errors and biologic variation have the effect of reducing the measured relationships, as they have been calculated in this discussion from single measurements on all subjects, normal or atherosclerotic. We have made an effort to assess these factors in order that the observed S_f 12–20 or cholesterol relationship to atherosclerosis may be corrected for attenuation.

The over-all reproducibility from one determination on an individual to a similar determination on that individual has a coefficient of reliability of 0.67 ± 0.05 for S_f 12–20 determination and 0.75 ± 0.07 for total serum cholesterol determination. (These figures represent the reliabilities over the one-year period during which the data reported in this paper were collected. During the same interval the technical reproducibility of the two measurements showed coefficients of reliability of 0.80 ± 0.04 for S_f 12–20 measurement and 0.91 ± 0.001 for serum cholesterol measurement. Therefore, it is estimated that the biologic variation during this period is expressed by a coefficient of reliability of $r = 0.84 \pm 0.06$ for S_f 12–20 measurement and $r = 0.82 \pm 0.07$ for total serum cholesterol measurement.

This may be translated into terms of observed biologic variation for the average "normal" (forty-one to fifty years) whose S_f 12–20 level is 45 mg. per cent. From the standard deviation of the distribution of levels ($\sigma = 24$ mg. per cent) and the reliability coefficient $r = 0.84$, we calculate a standard error of the obtained value of 10 mg. per cent S_f 12–20 lipoproteins. For serum cholesterol the average "normal" whose level is 243 mg. per cent, with a standard deviation of the cholesterol distribution of 51 mg. per cent and $r = 0.82$, will show a standard error of the obtained value of 22 mg. per cent cholesterol. Thus a single measurement places the average individual within $\pm$ 10 mg. per cent S_f 12–20 and $\pm$ 22 mg. per cent serum cholesterol of his "true" value for that particular year period two-thirds of the time.

For over-all variation, including biologic variation and technical errors of measurement, a single determination has a standard error of the obtained value of 14 mg. per cent S_f 12–20 and 26 mg. per cent serum cholesterol. Thus a single measurement places an individual (including both biologic variation and technical error) within $\pm$ 14 mg. per cent S_f 12–20 and $\pm$ 26 mg. per cent cholesterol of the "true" values two-thirds of the time.

It is to be noted that these are the reliabilities over the early period of this research and that current refinements of method have sizeably reduced the technical errors of measurement of S_f 12–20 lipoproteins such that the coefficient of reliability for technical errors alone has risen from $r = 0.8$ up to $r > 0.9$ at present. However, inasmuch as the data reported in this paper were collected over the past year, the lower value of r must be used in this analysis.

Currently in our laboratory both cholesterol data and S_f 12–20 data are being collected with coefficients of reliability (for technical errors alone) of over 0.90. A comment should be made about our estimate of the reliability of the cholesterol determination within our laboratory. This value is much higher than its average clinical reputation of the cholesterols determined in various laboratories. That poor reputation is undoubtedly due to the faulty procedures used in cholesterol determination within laboratories and the inconsistencies between different "accepted" cholesterol methods. The method we have employed (to be published elsewhere[15]) uses a KOH digestion before cholesterol extraction. This method, as the aforemen-

tioned reliability data indicate, gives a stable measurement.

We may now assess what all these reliability data infer for the relationship of S_f 12–20 lipoprotein and cholesterol measurements with atherosclerosis. The biserial correlation coefficients of Table v, when corrected for reliability, give rise to the values listed in Table vi.

TABLE VI

CORRECTED BISERIAL CORRELATION COEFFICIENTS FOR RELATIONSHIP OF S_f 12-20 LIPOPROTEIN AND TOTAL SERUM CHOLESTEROL WITH ATHEROSCLEROSIS

		$r^2 \times 100$
41–50 yr. age group		
Corrected biserial $r_{(chol.\ vs.\ atherosclerosis)}$	= 0.53	28
Corrected biserial $r_{(S_f\ 12\text{-}20\ vs.\ atherosclerosis)}$	= 0.76	58
51–60 yr. age group		
Corrected biserial $r_{(chol.\ vs.\ atherosclerosis)}$	= 0.35	12
Corrected biserial $r_{(S_f\ 12\text{-}20\ vs.\ atherosclerosis)}$	= 0.74	55

The computed biserial r's, even after correction for reliability, are still uncorrected for the impurity of the "normal" group (i.e., the inclusion of unknown atherosclerotics within this group) and the lesser impurity of the myocardial infarction group which is the result of diagnostic errors. In a previous section we estimated the purity of the normal group to be approximately 67 per cent, that of the myocardial infarction group is probably greater than 90 per cent. As a result of this the aforementioned crude accountability of differences between normals and myocardial infarcts will be increased by 20 to 40 per cent additional accountability. This may bring the true biserial r for the relationship of S_f 12–20 lipoproteins with atherosclerosis up to the neighborhood of 0.9.

By squaring the biserial r's of Table vi we obtain a measure of the relative accountability for the difference between atherosclerotics and normals, first for serum cholesterol determination and then for S_f 12–20 determination. It is seen from the values listed in Table vi that the S_f 12–20 measurement segregates atherosclerotics from normals between two and four times as well as does the serum cholesterol measurement. The observed correlation with atherosclerosis that cholesterol does have results almost completely from the partial association of the S_f 12–20 level and cholesterol level. This was the conclusion of the analysis of the data in the matched series and is also implicit in the regression lines for cholesterol on S_f 12–20 and S_f 12–20 on cholesterol. While there is a significant association of low serum cholesterol levels with low S_f 12–20 levels and high serum cholesterol with high S_f 12–20 lipoprotein levels, as we have stated on numerous occasions,[1,2,3] this relationship is so imperfect that at any serum cholesterol levels, even into the hypercholesteremic ranges, any values of S_f 12–20, high or low, can be and have been observed. (Fig. 3.)

By the method of partial correlations (subject to the same criticism as the biserial r's themselves plus a sensitivity to small errors in the values used), we have estimated the factors in the serum cholesterol-atherosclerosis association that might operate independent of the S_f 12–20 cholesterol association. The calculated first-order partial correlation coefficients obtained using the biserial r's from Table vi are as follows:

Partial r, for the relationship of serum cholesterol with atherosclerosis, nullifying the effect of S_f 12–20:

For 41–50 year group $r = 0.27$
For 51–60 year group $r = -0.03$

Partial r, for the relationship of S_f 12–20 lipoproteins with atherosclerosis, nullifying the effect of serum cholesterol:

For 41–50 year group $r = 0.68$
For 51–60 year group $r = 0.70$

The interpretation of these partial correlation coefficients indicates that most, if not all, of the observed association of serum cholesterol with atherosclerosis is accounted for because of the intercorrelation of serum cholesterol with S_f 12–20 levels. What little residual association the serum cholesterol shows with atherosclerosis cannot be proven significant from these data. In contrast, the S_f 12–20 relationship with atherosclerosis remains nearly at the same value, even after the interrelationship of S_f 12–20 and cholesterol is corrected for. While we would not adhere rigorously to the actual numerical values for these partial correlation coefficients (because of the limitations previously discussed), it is worth noting that they lead to the same conclusions concerning the relative associations of S_f 12–20 levels and serum cholesterol levels with atherosclerosis as were arrived at by comparing matched series of infarcts and normals within the same data (see previous section).

Changes in Blood Lipids and Lipoproteins with Age. It appears that the normal lipoprotein pattern in the human is one which shows components only below S_f 8 in appreciable concentrations. This pattern is the most frequent one observed

in a series of 140 normal boys and girls from 0–15 years of age, with no detectable age or sex difference within this age range.[16] Concentrations lower than 30 mg. per cent of S_f 12–20 lipoproteins are observed in 90 per cent of children; lower than 20 mg. per cent in 75 per cent of children. Both young men and women show similar patterns of lipoproteins and low levels of S_f 12–20 lipoproteins up to twenty-five years of age although there has been some increase from the levels of the 0–15 year old group. The male population from twenty-five to thirty years undergoes a striking transformation which elevates the S_f 12–20 level from a median concentration of 28 mg. per cent to 39 mg. per cent. Beyond thirty years of age the clinically normal male population shows almost no further significant change even through the sixtieth year. The normal female does not show the striking change from twenty-six to thirty years of age that is seen in the male. The female population increases slowly and steadily in S_f 12–20 level over the entire twenty-five to sixty year age span. A level essentially identical with that attained by the male population by thirty years of age is reached by the female during the fifty to sixty year decade. (Figs. 4 to 13.)

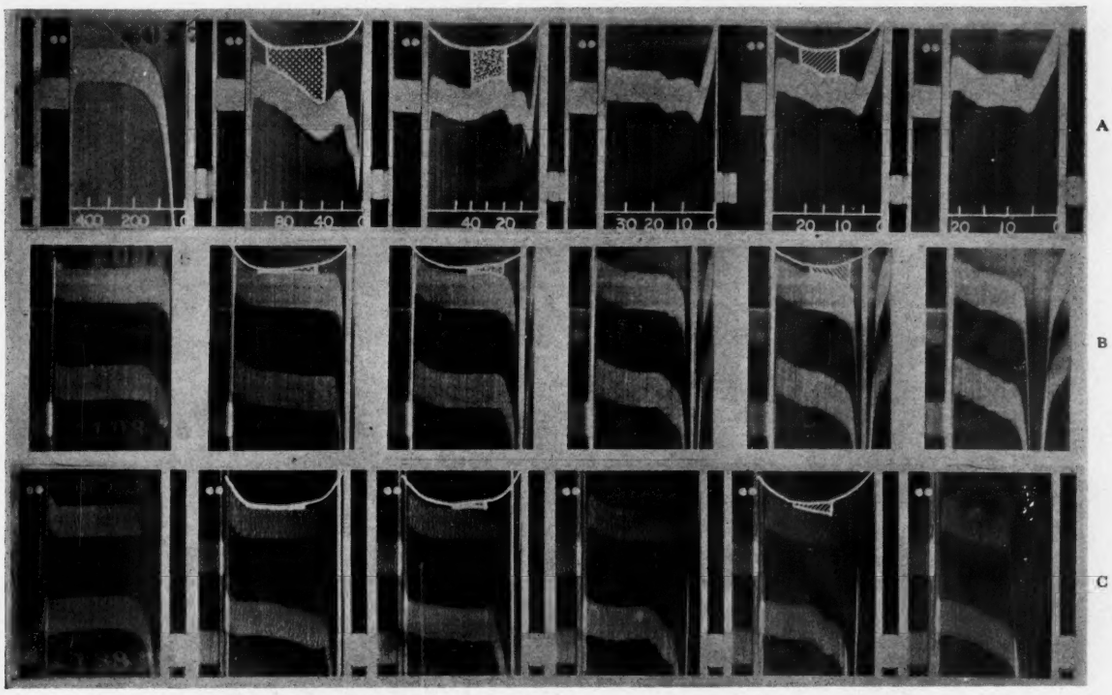
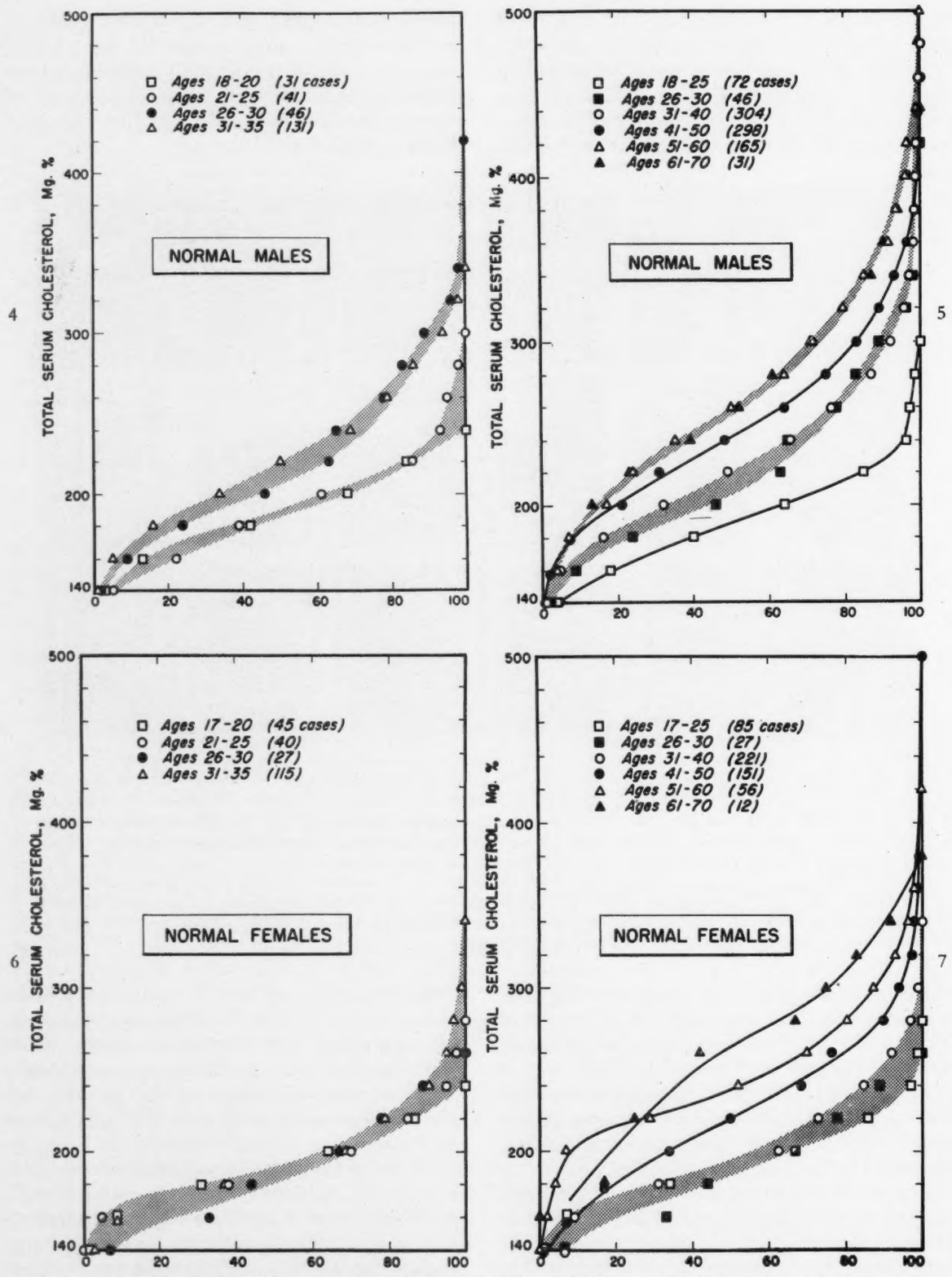


FIG. 3. The low interrelationship of S_f 12–20 levels with serum cholesterol levels obviously permits the frequent observation of high S_f 12–20 levels in the low range of serum cholesterol, and conversely the observation of low S_f 12–20 levels in the hypercholesteremic range. These are by no means anomalies due to random assortments of errors, and shown in this figure are representative illustrations of both situations. A, the pattern shown is from an individual for whom twenty serum cholesterol determinations ranged from 160 to 190 mg. per cent, and in whom the S_f 12–20 was always high, ranging from 70 to 90 mg. per cent. B, the pattern shows the converse situation in an individual with 46 mg. per cent S_f 12–20 and a serum cholesterol of 436 mg. per cent. C, the pattern shows a level of 20 mg. per cent S_f 12–20 lipoproteins at a serum cholesterol of 310 mg. per cent; six separate samples analyzed on this individual showed 300 to 320 mg. per cent cholesterol and always less than 30 mg. per cent S_f 12–20 molecules.

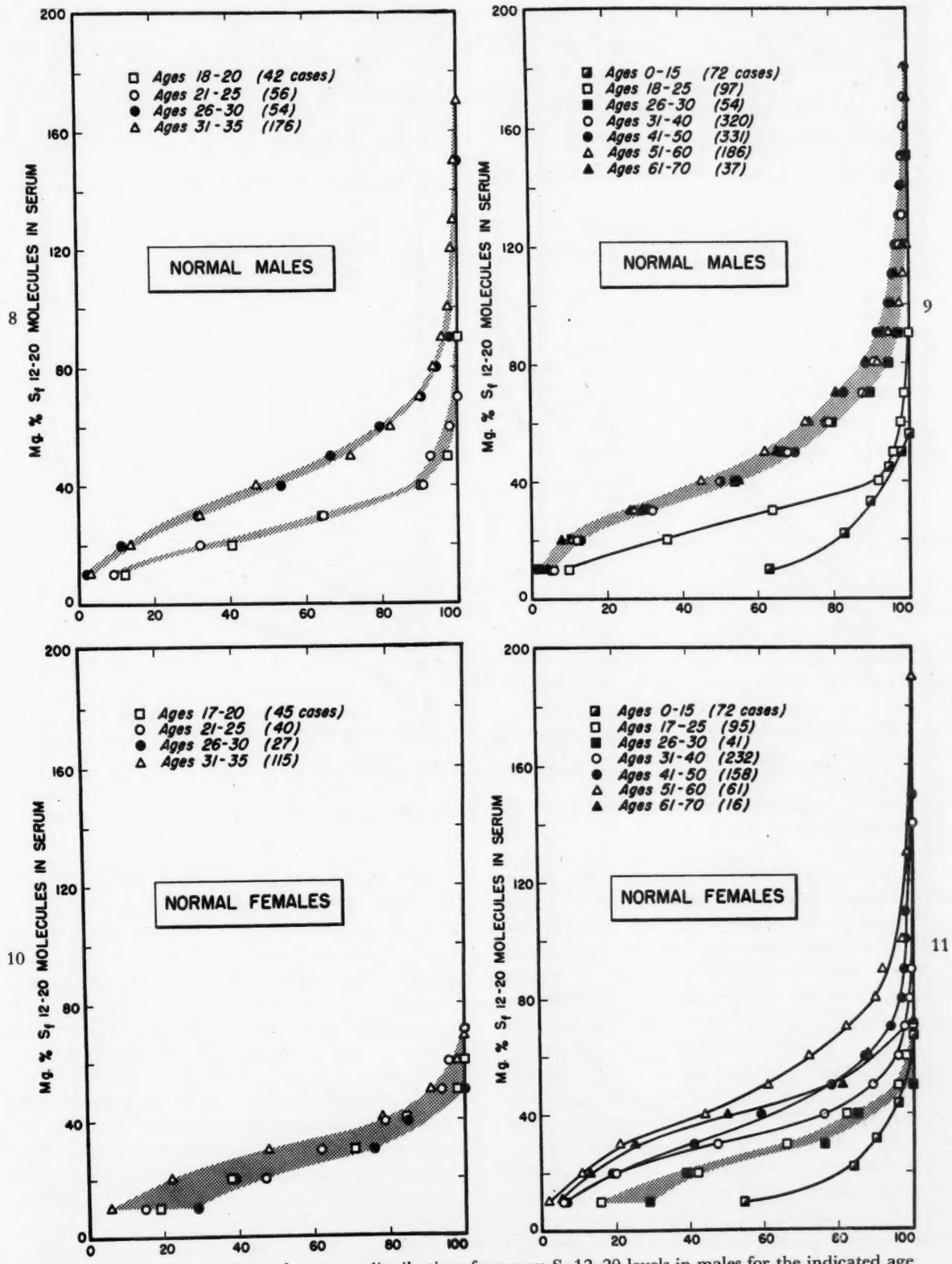
Serum cholesterol levels in males and females below twenty-five years of age are essentially identical. Both the males and females above thirty years of age show progressive and steady increases in serum cholesterol with age although the female remains lower than the male, at least to age sixty.

Males of the same age (thirty-one to forty years) and cholesterol level as a matched series of females show a significant ($p < 0.01$) elevation of S_f 12–20 lipoproteins, averaging 7 mg. higher than the female. This is further evidence that the male is more prone to develop the lipid metabolic defect that leads to the maintenance of elevated S_f 12–20 lipoprotein levels, since even



FIGS. 4 and 5. Accumulative frequency distributions for total serum cholesterol levels in males in the indicated age categories (normals).

FIGS. 6 and 7. Accumulative frequency distribution for total serum cholesterol levels in females for the indicated age categories (normals).

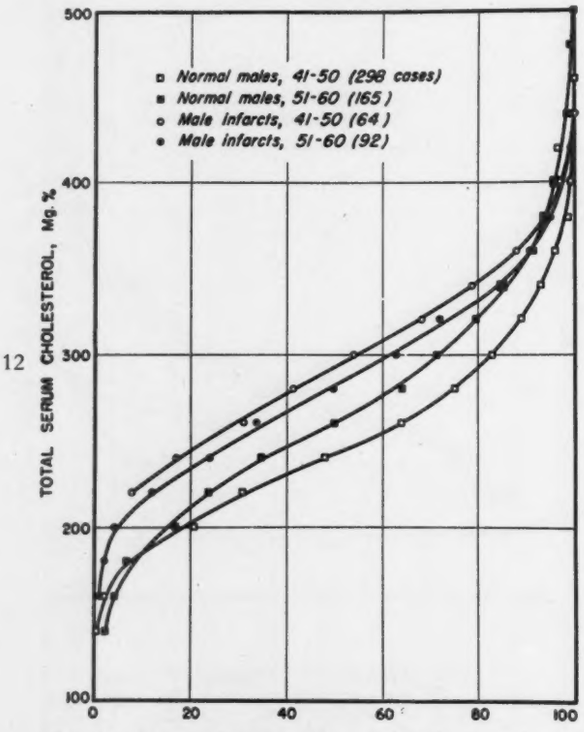


FIGS. 8 and 9. Accumulative frequency distributions for serum S_f 12–20 levels in males for the indicated age categories (normals).

FIGS. 10 and 11. Accumulative frequency distributions for serum S_f 12–20 levels in females for the indicated age categories (normals).

at the same total cholesterol, more of the cholesterol is in the S_f 12–20 fraction in the male than in the female.

The well known sex difference in the clinical sequelae of atherosclerosis, especially below the age of fifty, has aroused many speculations as to possible reasons for the difference. The clinical observations, however, are fully consistent with the trend of elevation of S_f 12–20 levels in the male. The male is exposed on the average (for a full twenty-five years beyond the age of twenty-five years) to a concentration of such molecules as great as the highest level reached by females (at age ~55). This is adequate explanation for the fact that the male under forty years of age shows approximately a twentyfold greater occurrence rate of myocardial infarction than does the female of the same age. Assuming a level of 60 mg. per cent S_f 12–20 as prognostic of rather active atherosclerogenesis, and comparing the males and females at thirty-one to forty years of age, the female has only 2 per cent of all its normals above 60 mg. per cent whereas the male population of the same age has 20 per cent of its members above this same level. This tenfold difference in numbers above 60 mg. per cent is in good agreement with the approximately twentyfold difference in occurrence rate of myocardial infarction at this age. At forty years of age 8 per cent of females are above 60 mg. per cent while 22 per cent of males are above this value at this age. The normal female has shown a rise from 3 per cent above 60 mg. per cent at average age thirty-five years to 28 per cent above 60 mg. per cent at average age fifty-five years. This ninefold increase in the per cent of the female population above 60 mg. per cent is consistent with the marked advance in frequency of clinical sequelae of atherosclerosis in the fifty to seventy year age category. The female at fifty to sixty years of age is essentially equivalent to the male of that age in S_f 12–20 level, or in atherosclerogenesis, so that each year that passes reduces the relative protection of her relatively lower atherosclerogenicity of earlier years. Thus it is not surprising that the ratio of clinical sequelae of atherosclerosis drops from approximately 20:1 below age forty to approximately 1:1 above age sixty years for males compared with females.



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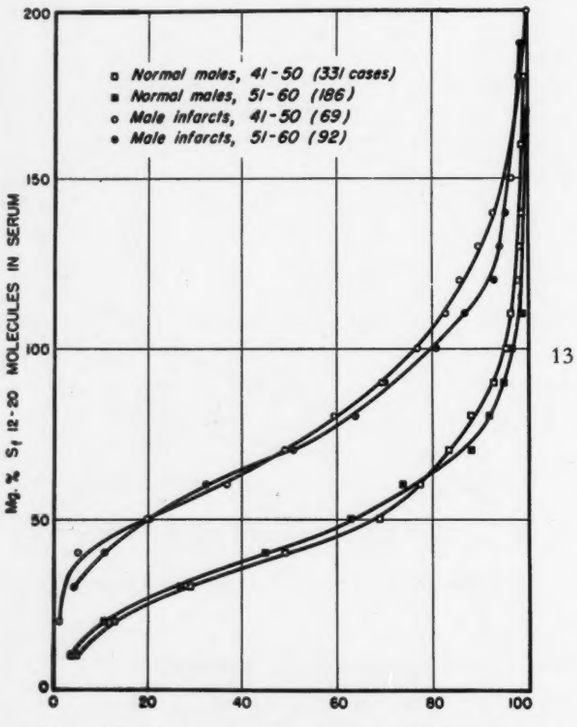

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FIG. 12. Accumulative frequency distribution of serum cholesterol levels in normals and myocardial infarctions (males).

FIG. 13. Accumulative frequency distribution for S_f 12–20 lipoprotein levels in normals and myocardial infarctions (males).

An interesting difference is seen between the increase in serum choesterol with age and the increase in S_f 12–20 with age. The S_f 12–20 level stops increasing rather abruptly at about thirty years in men in spite of the large surge of increase between the twenty-fifth and thirtieth year. The serum cholesterol, in contrast, increases steadily up to the fifty to sixty year age span. However, the evidence presented before showed that it is the male with high S_f 12–20 that is developing clinical sequelae of atherosclerosis so that he is constantly being segregated out of the population of clinically normal males. The average tendency for the male to increase in level of S_f 12–20 with increase in serum cholesterol would have resulted in a progressive rise in S_f 12–20 levels with age above thirty years. However, this rise is eliminated by the occurrence of such accidents as myocardial infarction so that a population equilibrium is reached with respect to S_f 12–20 level, thus maintaining the S_f 12–20 level constant even though the serum cholesterol level is rising steadily. (Fig. 14.)

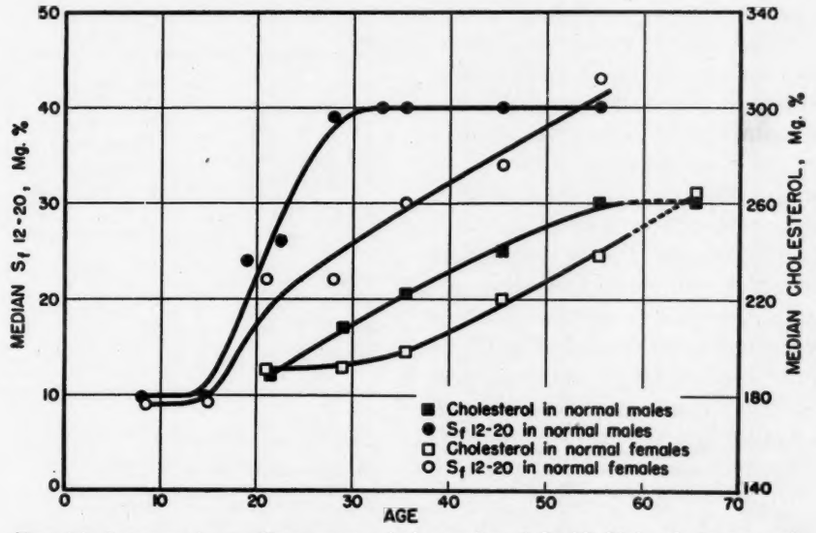

FIG. 14. Increase in median serum cholesterol and S_f 12–20 levels in normal males and females, with age.

SIGNIFICANCE OF S_f 12–20 LIPOPROTEIN LEVELS IN THE PROGNOSIS AND MANAGEMENT OF ATHEROSCLEROSIS

In the preceding section quantitative evidence has been presented for the relationship of S_f 12–20 lipoprotein levels to atherosclerotic activity. It follows, therefore, that the S_f 12–20 levels might be of prognostic value in patients with established atherosclerosis in assessing their present potential with respect to atheroma production as well as in normals with respect to predicting their likelihood of development of a clinical manifestation of atherosclerosis. We have sufficient follow-up data now to evaluate both of these possibilities.

Prediction of Occurrence of Myocardial Infarction in the Normal Population. A follow-up study has been in progress for the past year and a half to obtain information on the occurrence of clinical manifestations of atherosclerosis in individuals previously classified as normal and measured as to their S_f 12–20 lipoprotein level. At this time we have complete follow-up information from a block of 1,500 normal subjects studied. There have been four occurrences of myocardial infarction documented in males previously normal. These occurred at ages thirty-eight, forty-two, forty-five and fifty-three with S_f 12–20 levels of 100, 68, 55 and 52 mg. per cent, respectively. At the same ages in the normal group there are 1,000 cases, 340 of which were above 50 mg. per cent at the time of study and 660 were below 50 mg. per cent. While the number of cases of occurrence of myocardial infarction is small, the chance that the relationship between S_f 12–20 levels greater than 50 mg. per cent and occurrence of infarction is not significant is only one in fifty.

In a group of hypertensives (200) that had shown no clinical evidence of sclerosis at the time their S_f 12–20 levels were determined, there have now been three occurrences of myocardial infarction at levels of 55, 78 and 145 mg. per cent. These numbers are not significant by

themselves but they further show that 50 mg. per cent S_f 12–20 and above include the range of most probable occurrence of myocardial infarction since 50 mg. per cent is the 50:50 division of the hypertensive population. There are many uncomplicated hypertensives in the normal S_f 12–20 range.

Recurrence of Myocardial Infarction in Patients with Established Coronary Artery Disease. In a group of patients with previously known coronary artery disease a higher myocardial infarction occurrence rate is expected than in a normal population. We have now been able to observe thirty-nine recurrent myocardial infarctions in the over-all coronary disease population (359 cases) for which we have follow-up information over a one-year period. Of these recurrences thirty-six showed a level of S_f 12–20 lipoproteins at the time of initial study of over 50 mg. per cent and three were below 50 mg. per cent. (The actual levels in the recurrences were the following: 210, 156, 136, 136, 125, 116, 114, 114, 109, 101, 100, 97, 92, 88, 88, 88, 88, 85, 84, 84, 84, 83, 78, 78, 76, 76, 65, 65, 64, 62, 62, 61, 54, 52, 51, 50, 44, 43 and 38 mg. per cent of S_f 12–20 lipoproteins.)

We know no factors of difference between the over-all non-recurrence coronary population and the recurrence population, at least with regard to age, physical activity, sex, previous clinical history or drug therapy. Some of both the recurrence and non-recurrence group had been on low fat, low cholesterol diets. Since there are no significant differences between the two groups in other respects, it is justifiable to compare them on the basis of their initial S_f 12–20 lipoprotein levels. Considering a level of 50 mg. per cent S_f 12–20 lipoproteins, thirty-six of the recurrences were above this level and three were below this level, whereas in the non-recurrence group 202 were above this level and 118 were below this level. A test of significance of the relationship of levels above 50 mg. per cent with recurrence of myocardial infarction indicates there is less than one chance in 1,000 that this point of segregation is not real. An even more striking difference is seen above 80 mg. per cent when the recurrence and non-recurrence groups are contrasted. In the recurrence group twenty-two cases were above 80 mg. per cent whereas seventeen cases were below; in the non-recurrence group sixty-four cases were above 80 mg. per cent and 256 cases were below. A test of the relationship of S_f 12–20 levels above 80 mg. per cent with recurrence of myocardial infarction indicates there is less than one chance in 10,000 that this point of segregation is not real. These results may be converted to another form of some practical predictive value. The data are plotted in Figure 15 as the per cent chance of recurrence of myocardial infarction in one year as a function of a single measured level of S_f 12–20 lipoproteins (along with the data for occurrence of myocardial infarction in one year for individuals who have not previously manifested coronary artery disease). The plot indicates that for a patient with coronary artery disease the over-all chance of a recurrence within one year is approximately 16 per cent for an S_f 12–20 level of 100 mg. per cent whereas it is approximately 6 per cent for an S_f 12–20 level of 50 mg. per cent. These data show that the prognosis for a patient with coronary artery disease is much worse if the S_f 12–20 lipoprotein level is high than if it is moderate or low.

TABLE VII

Level of S_f 12–20 Lipoproteins (mg. %)	Cases Studied during Acute Phase who Survived No. of Cases 23	Patients Studied during Acute Phase who Died of the Infarct No. of Cases 26
Above 95.....	0	6
Above 80.....	0	13
Above 60.....	6	20
Below 60.....	17	6

A study of forty-nine patients in the acute phase of myocardial infarction shows that the S_f 12–20 lipoprotein level determined during the first week after occurrence (or from autopsy blood for some of the fatal cases) is of prognostic significance here also. The data are presented in Table VII.

It is seen that the levels are much higher in those not surviving the episode of myocardial infarction than in those who do survive. A significance test splitting the survivors and non-survivors at 80 mg. per cent gives a probability of one in 10,000 that the observed difference is not significant. Since the two groups were comparable in age, sex and previous history, it is justifiable to regard the only difference as the lipoprotein level difference. It will be noted that among the survivors the average level is lower than for those myocardial infarction survivors

studied at least six weeks beyond the acute phase. (Fig. 13.) We have frequently observed rises in level in a given patient after the acute phase of a myocardial infarction is past.[3] This probably indicates that in infarction survivors there is a lability of lipid metabolism incident to the acute insult, which in itself may have increased the chance of survival. From studies reported elsewhere[6] it seems possible that this lipoprotein alteration may be related to increased release of heparin or a heparin-like substance. The higher levels observed in the non-survivors suggests the possibility that the more extensive atherosclerogenesis and/or accumulated atheroma most likely present in this group has unfavorably influenced the prognosis.

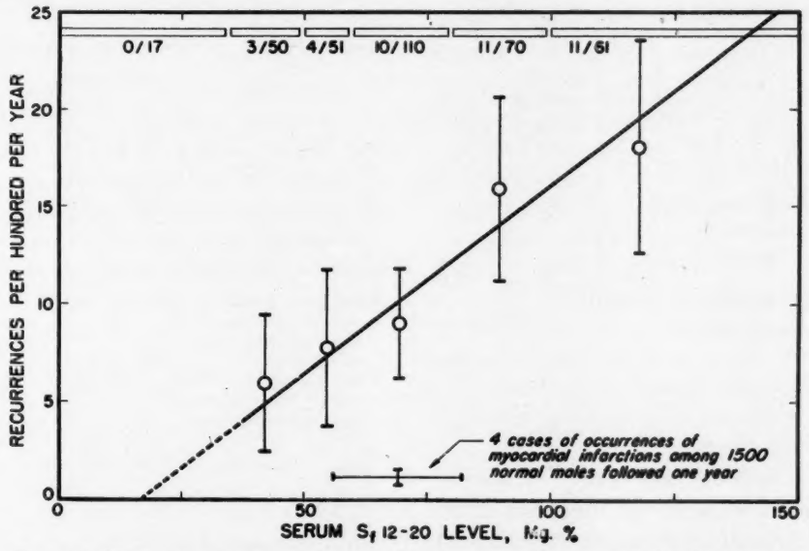

FIG. 15. Shows the per cent chance of recurrence of myocardial infarction in patients with coronary artery disease as a function of S_f 12–20 lipoprotein level. It is based upon thirty-nine recurrent myocardial infarctions in one-year follow-up of 359 patients with known coronary artery disease. The present best estimate for the position of the similar function for the occurrence of myocardial infarction *de novo* in normals is also shown.

The data on recurrences of myocardial infarction and the prognosis during the acute phase of an infarct indicate that the over-all outlook for the patient above 80 mg. per cent S_f 12–20 lipoproteins is quite poor when he develops coronary disease. It is, therefore, of real importance to evaluate the possibility of giving such patients some protection against their intense atherosclerotic activity, which we have considered a possibility by means of reducing the S_f 12–20 lipoprotein level via a reduction of the burden of dietary fat.

Dietary Restriction and S_f 12–20 Lipoprotein Levels. Our previous and continuing studies of controlled experimental groups have shown that it is possible in most humans to reduce the S_f 12–20 lipoprotein levels by restricting the total dietary fat and cholesterol intake.[2,3] We are fully cognizant of the evidence that fat and cholesterol are synthesized in the body but this is in no way inconsistent with the observed fact that a partial reduction in S_f 12–20 lipoprotein level is achieved by a reduction of total fat intake. The first analysis of a dietary follow-up among patients with coronary artery disease can now be made. Of special pertinence is a comparison of those patients with high S_f 12–20 lipoprotein levels who have experienced recurrent infarction during the period of follow-up with a group of patients of comparable levels who have not shown recurrence during the one to one and a half years of follow-up. The only therapeutic measure directed toward reduction of lipoprotein levels was the advice and directions for a low fat, low cholesterol diet. A diet of less than 50 gm. of fat and 200 mg. of cholesterol per day was advised, but it is evident that one cannot assess how rigorously a given patient adhered to this regimen. Therefore, the objective criterion of serial lipoprotein determination was used solely as the measure of dietary response.

Fifty-six cases of myocardial infarction with very high levels (above 80 mg. per cent S_f 12–20) followed with serial lipoprotein determinations

for one year are considered. Of this group there were sixteen recurrent myocardial infarctions during the one-year follow-up. Since the patient's statement as to adherence to a low fat diet is untrustworthy, we have eliminated such information from the analysis. A segregation of this group is presented only on the basis of the reduction or non-reduction of the lipoprotein level for the period of follow-up. In this sample it appears there is a differential favoring non-recurrence of myocardial infarction at any relatively reduced level of S_f 12–20 lipoproteins achieved by diet, but for the purpose of demonstrating a significant effect we have divided the group on the basis of whether the level has been reduced and maintained below 70 mg. per cent or whether the level has remained above 80 mg. per cent. Table VIII sharply defines the observed result.

TABLE VIII

	Recurrence Group	Non-recurrence Group	Totals
Cases starting above 80 mg. % S_f 12–20 and maintaining average level above 80 mg. %	16	26	42
Cases starting above 80 mg. % but reducing level and maintaining level below 70 mg. %	0	14	14
Totals	16	40	56

The probability has been calculated to be less than one in 100 that this segregation has occurred by chance. Therefore, the observation that the recurrences have been in the group that maintained a high level is highly significant, and we can conclude that dietary reduction of S_f 12–20 level has given significant protection against recurrence of myocardial infarction during the year period of observation.

The various groups shown in Table VIII turn out to be closely matched for initial S_f 12–20 levels. (Table IX.) The only exception is the non-recurrence group which started above 80 mg. per cent and reduced to an average level below 70 mg. per cent. Here the slightly lower initial level (8 mg. per cent) is the result of the lack of a single matched case at 200 mg. per cent in this group compared to the other two groups.

POSSIBLE NATURE OF THE BASIC LIPID METABOLIC DEFECT ASSOCIATED WITH ABNORMAL SERUM LIPOPROTEIN TRANSPORT

In an earlier section of this article the concept was presented that elevated levels of such lipoproteins as the S_f 12–20 class represent a reflection of a lipid metabolic defect. The basis of this lipid metabolic error is a crucial factor both in the understanding of fat metabolism itself and in its relationship to atherosclerosis. The recent work of Graham et al.[6,14] has demonstrated that heparin can profoundly influence blood lipid transport in the rabbit and human, operating in a manner that suggests facilitation of handling of fat and that results in various degrees of alteration of serum lipoprotein transport toward a normal pattern. The significance of such alterations in lipid metabolism by heparin administration is now evident from Graham's demonstration that atherosclerosis in the cholesterol-fed rabbit can be suppressed by heparin. In the human a finding paralleling the serum lipoprotein changes induced by heparin is the genuine relief of angina pectoris noted in patients with this symptom who receive heparin intermittently in 25 to 100 mg. doses one or two times per week. The long duration of this effect and small doses of heparin required do not argue for either an anticoagulant or vasodilator action. While many of the changes in lipoprotein metabolism following heparin are rapid (minutes to hours), other phases of the heparin effect, which can be followed by serial ultracentrifugal studies, show maintained or progressive changes over periods of days. The individual response to heparin administration is complicated, involving transformations extending over the entire lipo-

TABLE IX

	Recurrence Group			Non-recurrence Group		
	Initial Level	Average Level	Per cent Reduction	Initial Level	Average Level	Per cent Reduction
Cases starting above 80 mg. % and maintaining average level above 80 mg. %	112	105	6	116	99	15
Cases starting above 80 mg. % but reducing level and maintaining level below 70 mg. %	...	...	..	104	57	50

protein spectrum. There is great individual variability in the lipoprotein response although we have yet to see a single human (of seventy-five) who did not show some alteration in serum lipoproteins as a result of heparin administration. Inasmuch as this agent is the most striking yet observed which shifts lipoprotein transport in the direction of normality, especially in those individuals manifesting severe degrees of the lipid metabolic disorder, it is plausible to suggest the hypothesis that a deficiency of heparin (or some agent of similar properties) is one of the prime underlying factors involved in the lipid metabolic defect itself. It is also important to evaluate the possibilities of clinical control by heparin of the lipid metabolic error which results in atherosclerosis. Such studies are now in progress.

SUMMARY

1. Serum lipoprotein patterns as studied ultracentrifugally in the human indicate lipoprotein transport may be interpreted as reflecting varying degrees of a lipid metabolic error.

2. The nature of several lipid transport disturbances have been described for a variety of experimental procedures in the rabbit. In all disturbances there is a strong positive correlation between elevation of the S_f 10–30 class of lipoproteins and the rate of development of atherosclerosis. Lipoproteins of the classes of S_f 10 and less and S_f 40–50 and higher do not show this correlation. Total serum cholesterol is positively related to the development of atherosclerosis only in those experimental procedures which allow for the increased serum cholesterol to be largely in the S_f 10–30 class.

3. A critical comparison has been made, in which the analysis of total cholesterol and S_f 12–20 lipoproteins was done on aliquots of the same serum sample, of both levels in normals vs. atherosclerotics, using myocardial infarctions as the test group. The over-all correlation of S_f 12–20 lipoprotein levels with atherosclerosis is two to four times as great as that for serum cholesterol levels with atherosclerosis.

4. The S_f 12–20 lipoprotein levels are associated with atherosclerosis, independently of their relationship with serum cholesterol. The S_f 12–20 levels account for the bulk of the over-all predictive segregation of atherosclerotics from normals.

5. The serum cholesterol level is very much less, if at all, associated with atherosclerosis, when considered independently of its association with the S_f 12–20 levels.

6. One-year follow-up studies of patients with coronary artery disease indicate that early recurrence of myocardial infarction is significantly associated with elevated S_f 12–20 lipoprotein levels. An approximate estimate of recurrence rate as a function of S_f 12–20 level may be made from the data on thirty-nine recurrences in the follow-up study. At 50 mg. per cent S_f 12–20 the chance of recurrence is ~6 per cent in one year; at 110 mg. per cent the chance is ~18 per cent.

7. In acute myocardial infarction the prognosis for survival is worsened with highly elevated S_f 12–20 lipoprotein levels, as determined during the acute phase.

8. Follow-up studies show that the reduction of S_f 12–20 lipoprotein levels by dietary restriction of fats and cholesterol gives a significant degree of protection against recurrent myocardial infarction in patients with coronary artery disease whose levels before dietary restriction ranged above 80 mg. per cent.

9. The only pharmacologic agent which rapidly shifts the lipoprotein pattern in humans in the direction of normality is parenteral heparin. The possibility is considered that a deficiency of heparin or a heparin-like substance may be involved in causing the basic lipid metabolic defect in humans.

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Clinic on Psychosomatic Problems

Psychotherapy of a Psychosomatic Illness: Essential Hypertension

THESE cases are chosen to illustrate the relation between psychiatric and medical factors in the production of symptoms. They are part of the Harvard teaching on the Psychiatric and Children's Medical Services of the Massachusetts General Hospital. These psychiatric conferences are edited by Drs. Stanley Cobb and Henry H. W. Miles. Publication is made possible by a grant from the Josiah Macy, Jr., Foundation.

DR. HENRY H. W. MILES: The patient to be presented today is Mrs. H. R., a thirty-five year old married woman, who has been particularly interesting to me for several reasons. She has been treated for almost four years now with a gradual evolution of definite personality changes. Second, psychotherapy has been a cooperative job with a social worker also seeing the patient, and for a time her eight year old son was treated in the Child Psychiatry Clinic. Finally, there are provocative implications as to the significance of her hypertension although it has not been an important feature clinically.

When Mrs. R. was referred to us she had many complaints, chief among which were resentment and depression. She said, "I feel so bitter; I resent everything. I resent my child, my husband and I resent being crippled." There were frequent spells of depression with weeping and feelings of hopelessness. She also had symptoms of fatigue, muscular weakness, insomnia and indigestion. She was known to have moderate hypertension but was not concerned about it.

As with so many of our patients, it was difficult in this instance to establish any definite "present illness" since her problems dated back to childhood; therefore, it is perhaps best to begin with the family constellation, then give a brief chronologic account of her life experiences, with pertinent excerpts from the interview material. Therapeutic sessions were carried out once a week for about two years (with long summer vacations) and in the past two years these sessions have taken place about every other week. This was partly a matter of expediency since the patient lives fairly far away and cannot easily make the trip more than once a week.

The patient is the third of five siblings of whom a brother two years her senior has been the most important to her. The parents belonged to a very strict religious sect, the father being a stern intolerant man who in his youth had gambled and dissipated. The patient remembers that her father spanked her frequently because she was so rebellious and "full of the devil." The mother was a nervous woman whose overprotectiveness and fears in regard to her children's safety gave indirect evidence of her underlying hostility. She had had hypertension for an unknown number of years. (An illuminating incident was reported after two years of therapy. The patient one day asked her mother, "Did you give me much love when I was little?" Replied the mother, "I gave you food and clothing, but I don't think I ever told you I loved you.")

The patient suffered from a congenital hip deformity (coxa plana) which necessitated a built-up shoe. She had a good deal of pain and limitation of activity but the parents paid little attention, regarding the deformity merely as God's will. The mother would never permit the patient to be hospitalized for orthopedic treatment as she was afraid the doctors "might experiment on her." Socially, the patient led a restricted life and suffered from feelings of shyness and inferiority. She graduated from high school and was greatly disappointed at having to forego college because she was "lame." Her parents did not allow her to have dates and the only young men permitted to call were ministers or theological students. She was married at twenty-one to a young minister of her parents' choice and had much difficulty adjusting herself sexually. Even kissing made her "grit her teeth"

and feel nauseated. She became pregnant four years after marriage in the face of her family's warning, "the baby will be deformed like you are." The pregnancy was a difficult one with much nausea and vomiting. It was interesting that elevated blood pressure was first discovered at this time. For reasons unknown to us a cesarean section was performed. The patient was unable to nurse her baby and had marked fears of dropping him. She developed a postpartal psychosis with auditory hallucinations and fears that someone would kill her. These disappeared within a couple of weeks, but the patient always found it an exhausting task to care for her son. When he began to walk it was discovered that he had a hip deformity like the patient's, and when he was four he had to spend a year in a body spica and an orthopedic frame. The patient felt "trapped," tied down and very resentful yet at the same time terribly guilty. She was sure that his deformity was due to some fault of hers. About this time her husband was pastor of a congregation composed largely of Indians and Negroes. The patient became very much frightened of them, especially of the Negroes. There was a decidedly paranoid coloring to her fears: "they" wanted to get rid of her; "they" were saying this or that; "they" thought she was too "worldly." She became so depressed, anxious and fearful that her husband (upon the advice of a physician) gave up the ministry, moved to a different town and got a job as an office worker. It was soon after this that she was referred to our Psychiatric Clinic.

Physical examination was done in the Hypertension Clinic and revealed nothing abnormal except the hip deformity and a blood pressure of 168/100. Routine laboratory studies, including urinalysis, kidney function tests, blood chemistry, Hinton test and chest x-ray were within normal limits. (Her blood pressure was checked at intervals for the next three years and did not change appreciably. Individual readings ranged from 150/90 to 185/110 but the mean level remained about the same, approximately 150/100.)

Psychiatric Interviews. The patient was always neatly and attractively dressed and had a rather provocative manner. She smiled a good deal and blushed easily. A striking feature of the therapy has been her marked inability to verbalize feelings and fantasies. It has been difficult at times to decide whether there was conscious withholding of material or whether there was simply a tremendous amount of "nonverbal" emotion, not capable of being expressed in words or images.

At first we talked mostly about her feelings of resentment. There was great hostility in her relationships to her husband and to her son. She felt extremely guilty because her religion teaches that such thoughts are wicked and wrong. Then she began expressing complaints: her husband did not really care for her; he would never take her with him when he went out in the evenings; he gave too much time to the church. She also felt that he acted in an unbecoming manner with other women, that he permitted them to act "silly" and did not "keep them in their place." The complaints gradually shifted to the therapist; she was very angry because I never *did* anything to help her. "You just sit there and talk to me." She said that every visit to the clinic made her feel worse and she threatened to discontinue treatment, at the same time always showing up punctually for appointments. (From the emotions that she could verbalize, one caught a glimpse of intense and destructive fantasies of which she was only partially aware. Her expressions were of interest: "I could bite your head off" or "I could claw your eyes out." It was my belief that the feelings were of such disturbing primitive quality that she could not tolerate them in full consciousness.)

As the doctor-patient relationship developed, her ambivalent feelings were more marked. She was reluctant to admit any warm feelings for the therapist although they were obvious, and when I commented on them she became very angry and depressed. She accused me of being conceited and also feared that I would be angry at her or ridicule her. Only after several months of treatment was she able to tell me of an episode with her brother which had occurred when she was seven years old. He had persuaded her to take his penis in her mouth and then when their mother had discovered it he had tried to put the blame on her. (This experience with her brother was very useful in interpreting and working through some of the feelings which she had attached to me and had been unable to admit.) For a long time she had produced little material in the interviews other than complaints about her symptoms, her hostility toward me and her conviction that I was not interested, that I did not care whether she got well, that I would make fun of her, etc.

The patient then recalled a sudden change

which had occurred in her father's behavior when she was about twelve. This was when her breasts began to develop and she spoke with much emotion of her shame because they were "so large." Her father had always permitted her to nap with him on the couch on Sunday afternoons and without explanation he stopped this. She was hurt and puzzled. Again the material contained many allusions to her sexual feelings and the intense reaction of disappointment and rage which masked the incestuous wishes in regard to her father.

As the patient felt safer with us, she was able to talk about her son who had enuresis and showed a good deal of uncontrollable aggression. She now could admit that she had never wanted a baby and that she resented having to care for him. With this acceptance of her negative feelings she was able to make arrangements for his treatment in the Child Psychiatry Clinic and over a period of months it was interesting to us to observe the parallel fluctuations in their symptoms. As she improved, so did the boy; and on several occasions when she had a temporary period of severe tension, anger and depression, her son began wetting the bed again.

During the next couple of years there were many vicissitudes: The patient had to work through her resentment when her husband became interested in another woman; she was involved in a minor traffic accident and "acted out" her ambivalent masochistic fantasies by going through an unnecessary operation and becoming embroiled in a law suit. Gradually, however, she was able to understand more and more that these "acts of fate" were really related to her own unconscious impulses. The positive aspect of her relationship to me became much stronger and she was increasingly aware of it. She said on one occasion, "I wish I could just get into your pocket and go home with you." As we discussed her feelings of wanting to be protected and loved, she was able to verbalize more clearly the fears of rejection and ridicule which were the source of her anger. The fantasies of wanting to be protected, to be dependent on me, gradually changed to more frankly heterosexual wishes. These came out indirectly in fears that men were looking at her with sexual intentions (which was probably true as she frequently managed to appear quite seductive) and finally she admitted having a dream in which she had intercourse and enjoyed it very much. This was a new experience for her as with her husband she had always been completely frigid.

After the third year of treatment the patient decided that she would never be able to leave her husband and that she might as well make the best of the situation. Despite her turmoil when she found out that her husband had been unfaithful, she carried on well without serious symptoms and finally got a job to keep herself occupied. She also attended business courses a couple of nights a week and enjoyed them. Interestingly, as she felt better and had conscious sexual desires, her husband's interest and potency waned. In the interviews we were able to discuss with more mutual understanding her dependent needs and how she really had never had any real gratification from her mother, or later her brother and father. Her behavior and fantasies were now much like those of an adolescent girl. She felt excited sexually by men and acted in a teasing and provocative way with her employer and with the men she met at work. She "acted out" her anger and resentment toward her husband by flirting with men in his presence, consciously in an innocent way, but with the result that he became impotent. In her fantasies she was bigger and stronger than he and when I asked if his refusal to kiss her was because he was afraid she laughed and said, "that's silly." She then confessed that at times she had bitten him and that the biting was not always entirely playful. (This seemed to be the conscious expression of the deeper, intense aggressive impulses.)

When I suggested to her that we spend the last few months of therapy in working toward the goal of ending treatment, she became extremely upset. She was hurt, angry and depressed. Her associations led back to her brother (who had seduced her and rejected her) which again highlighted the transference situation in which she felt so desperately unhappy to be deserted by the therapist to whom she had become so attached. However, we have been able to deal with this satisfactorily and now I think she is able to carry on with her husband and son. She still has very ambivalent feelings toward the former but can handle them fairly realistically. Her relationship with her son is much better and he in turn has been behaving well for the past year or so. Symptomatically she is greatly improved and her depressions are brief and no longer severe.

I will summarize now the role of the social

worker in the treatment. Usually after her interview with me the patient would see the social worker for a discussion of current problems. Sometimes she utilized these sessions to talk of her feelings toward the therapist but usually discussed such things as how to manage her son or the restrictions imposed by her conscience. She felt very guilty even for wearing lipstick and earrings and was reassured that this was not immoral. The social worker was able to help her achieve some independence from her over-rigid conscience and at the same time exercised control of her tendency to "act out" her impulses by discussing the possible consequences of certain courses of action. It was our impression that this safe (and gradually quite friendly) relationship with another woman meant a great deal to the patient and was a new and educational experience for her.

PRESENTATION OF PATIENT

The patient was interviewed by Dr. Lindemann and talked freely about her problems. She admitted being afraid to give up therapy but said that she felt she had been helped a great deal. She was told that in case there were unexpected complications or problems the "door was not closed to her,"—that she could return to the clinic for advice or further help.

DISCUSSION

DR. ERICH LINDEMANN: That was a very interesting presentation and in a way it is self-explanatory. Everything becomes so clear as one goes along that I hardly know which point needs elaboration.

DR. MILES: I have been interested in what has happened in the dynamic sense. A very important figure in her early life was the brother who seduced her and then rejected her. Two months ago when the subject of ending treatment was first broached, her immediate response was to get very angry and depressed; she said she would not come any more but of course she did. She then talked quite spontaneously about James, her brother, who has been in India for the past fifteen years. She had not mentioned him for at least two years. She wondered whether he really liked her or not. She recalled that after the sex play he had been disgusted with her. He absolved himself of the guilt, blaming her for the episode. This seemed to have set the pattern of her heterosexual relationships which were characterized by so much repression of the positive feelings and so much anger toward men.

We never worked intensively on her early relationship to her mother, which must have been the basis of the "oral aggressive" impulses. These very strong feelings of rage could be explained by the early frustration of her dependent needs. During the course of treatment there seemed to be a shift or development from the intensely ambivalent hostile-dependent relationship to a more grown-up relationship, rather like that of an hysterical girl. She still has feelings of anger and depression, feelings of not trusting people and not being sure that they like her, but these are not nearly so prominent as they were. Heterosexual fantasies are now more prominent. She has been able to achieve some sexual satisfaction but is still partly frigid. The changes which have occurred must be related to the fact that she has learned in the therapeutic relationship that all men and women are not just like her brother and mother.

DR. LINDEMANN: If she had worked with you alone without the social worker, it might not have turned out as well. She is a person who "acts out" in a big way. She was able to go to the social worker after her interview with you and tell of her experiences with the psychiatrist. The drive to enact what she wished to enact in transference was great. She might have smashed the marriage if there had not been an acceptable woman to talk with after the interview with you. This arrangement let her make the grade and has been helpful. The whole treatment plan was a joint operation of psychiatrist and social worker. The intention was to protect this very emotional patient, who has such a hard time coping with herself, from excessive masses of feelings which would have swamped her. The psychiatrist and social worker were friendly but firm people who discussed certain topics and plans with her. This limited setting is a helpful complement to the less *educative* effect which the psychiatrist has. The psychiatrist often appears to the patient as a person who opens wide the door to any kind of emotional behavior. In a patient of this type, the danger is obvious. One good way of dealing with it is the participation of a social worker in the program.

This patient was so vulnerable that we wonder if a very important determinant was the narcissistic injury caused by her deformity. The parents did not have the capacity to work things through with her when she was a child. The

mother was not concerned with her and the father did not have any decent program of action. The deformity was not noticed by the family, except that the parents were uncomfortable about it. She had no adequate relationship with her parents. The patient was foiled by her mother's inability to express warm feelings toward her. The father was thrown back and forth between positive feelings toward the child and feelings of restraint because of fear that his feelings might be misinterpreted. This is often seen in fathers of hysterical girls. This behavior was probably another source of the transference material. The patient had to test the therapist in a variety of ways, in many situations and wondered whether he would be like her father in some circumstances or not.

Her therapist remained friendly, interested and eager to find a joint solution with her. He did not get involved with her in any dangerous emotional ways; and the patient had an awareness of the therapist's feelings, too. She felt he was a safe person to be with—a good parent. This testing comes about through the patient's creating situations which are challenging to the therapist. When she is safe with her therapist, she can be friendly with her husband again and he regains his potency once more.

The husband must be quite a fellow. She is quite right about him now—to turn to him now. He seems to have stood it quite well without being too troubled. Did he need reassurance?

Miss Marianne Richardson: Mrs. Springer saw him twice and he asked, "Is she going to get better?" He was reassured that she was getting better and asked to bear with us for a little while longer. The patient was angry when the social worker saw her husband.

Dr. Lindemann: He seems to have been a devoted husband.

Miss Richardson: I think he really is.

Miss Sylvia Perry: The social worker was giving the patient permission to do things she was not permitted to do before, so the relationship included permissiveness in some areas and limitations in others. The social worker showed her confidence that the patient could do things for herself.

Dr. Miles: Our limitation of her actions was more in the area of the sexual impulses by pointing out to her the sort of consequences which might follow certain behavior.

Dr. Lindemann: The hypertensive factor is a very minor aspect of this case. It would involve discussion which would not be particularly relevant here.

COMMENT

This case discussion was focussed upon the therapeutic technics employed in long-term psychotherapy of a woman with a severe neurosis and moderate arterial hypertension. The presentation was aimed at showing how psychiatrist and social worker cooperated in the treatment process with some interpretation of how we believed the therapy helped the patient. One of us (H. H. W. M.) has been particularly interested in the psychiatric aspects of cardiovascular disease; and while this patient's hypertension was not a significant factor in her symptoms or in her disability, it nevertheless was of interest from a theoretic standpoint.

It has been recognized widely that patients with essential hypertension have many personality problems. In classic papers which should be read and re-read by physicians who treat hypertensive patients, Ayman[1,2] clearly showed that most of the early symptoms of hypertension are unrelated to the level of the blood pressure, and that any form of treatment which is prescribed with enthusiasm and conviction will alleviate a large percentage of the symptoms. The importance of repressed hostility resulting from frustration of dependent needs has been suggested as a factor in the production of hypertension.[3,4]

From a review of the literature, including animal experiments, and from psychiatric observations on about forty hypertensive patients[5] it has been my impression that the emotional factors in hypertension, while not specific, do have certain characteristics which are not typical of the ordinary psychoneurotic patient. The broad view of certain psychosomatic illnesses, as "diseases of adaptation" as Selye[6] puts it, has a pragmatic value. Chronic stress can be thought of as producing certain effects upon the

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individual which may vary according to the specific characteristics of that individual: his hereditary susceptibility, his characteristic patterns of meeting life situations and perhaps also specific biologic idiosyncrasies, e.g., in the structural and physiologic make-up of the adrenal cortex.

There is evidence that in certain persons not only chronic rage but also other strong emotions as fear or anxiety or physical trauma, such as exposure to cold, can produce hypertension. Whether this is the same as "essential hypertension" is not known. It has been my impression, however, that a rather characteristic feature of many patients with hypertension is the *intense* character of their emotions. Often this is apparent to the therapist who may feel frustrated because the patients do not seem able to verbalize their feelings. The more one works with these patients the more one is impressed with the "primitive" quality of the emotions. This is essentially what the psychoanalysts mean by "hostility due to frustration of oral dependent needs." In the light of Selye's theory and the above mentioned evidence it seems possible that most important in the psychologic sphere is the *intensity* of the emotional stress rather than its *specificity*. That is to say, "primitive" inarticulate rage is a more powerful stress than is the anger of the well adjusted person or the ordinary psychoneurotic. (Also intense fear as in prolonged battle experience or exposure to extreme cold is a stress of a degree not found in ordinary life.)

This patient certainly had intense emotions and it is interesting that her elevated blood pressure apparently began when she was pregnant. Not only was there the physiologic stress of pregnancy but also the strong feelings of resentment at being pregnant and guilt because of the resentment.

Without holding any brief for Selye's theory, it does seem to explain many empirical observations, and seems to us to offer much help in understanding the arterial hypertension (along with the neurotic symptoms) as a mode of adaptation, or vital expression of the total human organism, in response to the internal and external stresses which it encounters during its life span.

From the standpoint of the psychiatrist, one treats the patient's personality problems; if medical therapy is indicated, that can be managed concomitantly by the internist. Obviously when irreversible changes have taken place in the vessel walls one will not affect the level of the blood pressure by psychologic means. A succinct discussion of what one may expect from psychotherapy is given in a brief but excellent paper by Binger.[7]

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Clinico-pathologic Conference

Recurrent Hematemeses, Abdominal Pain and Hepatic Failure

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D. and David E. Smith, M.D., of weekly clinico-pathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine by Junior and Senior students.

THE patient, M. B. (No. 101845), was a white married pharmacist, sixty-six years of age, who entered the Barnes Hospital for the first time on November 18, 1942, complaining of abdominal pain of eleven days' duration. The family history was non-contributory. The patient's general health had been good until 1937 when he had a "nervous breakdown," characterized by depression and by visual and auditory hallucinations. He remained at home under the care of a physician and a nurse for about six months, and subsequently was able to return to work. Although he apparently was "moody and gloomy," he worked regularly; he ate an adequate diet, smoked several cigars daily and took an occasional highball. He had never had jaundice.

In 1939, without premonitory symptoms, the patient suddenly vomited bright red blood. A similar episode occurred early in 1940 and he was admitted to a University Hospital in another city. There he was found to have ascites and "secondary" anemia; a diagnosis of Banti's syndrome was made. Splenectomy and omentopexy were performed. The patient's postoperative course was uneventful but he never again regained his former strength. Following the operation he had two more bouts of hematemesis, the last in February, 1942. Neither was severe enough to require transfusion. In the eleven days prior to his first Barnes Hospital admission the patient was troubled by a dull constant pain in the upper abdomen. He stated that his abdomen felt "large and tight." Concomitant with the pain he became anoretic although previously his appetite had been good. He had been free of other significant gastrointestinal symptoms except for slight epigastric discomfort after eating fatty foods.

At the time of entry physical examination revealed the temperature to be 36.4°C., pulse 80, respirations 18, blood pressure 130/80 and weight 134 pounds. The following positive findings were noted: The patient was edentulous. There were several small, non-tender lymph nodes in the left axilla, measuring 0.5 to 1.0 cm. in diameter. The fingers were clubbed. The liver edge was thought to be palpable 3 cm. below the right costal margin. Abdominal examination also revealed shifting dullness but no fluid wave. There was slight enlargement of the prostate.

The laboratory data included the following: red blood cell count, 4,240,000; hemoglobin, 12.7 gm.; white blood cell count, 5,000; differential count, normal. The urine showed a specific gravity of 1.022 and 1+ proteinuria, but was otherwise negative. The blood Kahn test was negative. The total proteins were 6.6 gm. per cent with 3.8 gm. per cent albumin and 2.8 gm. per cent globulin. The non-protein nitrogen was 20 mg. per cent. There was no bromsulphalein retention at the end of thirty minutes. A gastrointestinal x-ray series was indeterminate.

The patient's hospital course was uneventful and he was discharged on November 21, 1942.

During the next two years he apparently was free of abdominal discomfort. In April, 1943, he was admitted to another local hospital where he was given sulfathiazole for "left upper lobe pneumonia." In September, 1944, he had a massive hematemesis, and was re-admitted to the local hospital in shock. At that time his red blood cell count was 2,480,000 and hemoglobin 7.3 gm. He was treated conservatively and responded satisfactorily.

In January, 1945, he again developed dull,

cramping, right upper quadrant pain which did not radiate. He was admitted to another outside hospital in July, 1945, because of increased severity of the pain and the additional complaints of chilly sensations and fever. On several occasions prior to admission his stools had been tarry and several times had contained bright red blood. A cholecystogram was said to have shown a pathologic condition of the gallbladder and the patient was subjected to exploratory laparotomy. At operation the peritoneum was found to be thickened and 500 cc. of straw colored ascitic fluid were present. There were adhesions between the right lobe of the liver and the abdominal wall and colon. The gallbladder could not be visualized. The liver extended about 2½ cm. below the costal margin and was described as "dark purple in color and hobnailed." A liver biopsy was taken and was said to have shown "chronic periportal hepatitis and perihepatitis." The patient's postoperative course was stormy and was complicated by bronchopneumonia.

A few days after he was discharged from the hospital he developed two "blisters" lateral to the abdominal scar. These lesions were drained but the patient developed an area of swelling along the right costal margin which was likewise opened; a large amount of purulent fluid was obtained. Subsequently, a sinus tract persisted and drained intermittently a small amount of fluid which was never bile-stained. The patient also developed a ventral hernia about this time.

He had two further episodes of hematemesis, the last in 1946. After the death of his wife in 1947 he went to live with his son in a local hotel, and his diet was less well controlled from then on. In the fall of 1949 he began to have right lower quadrant or epigastric pain which came on about one-half hour after meals and was associated with some eructation. The pain was described as "sharp" in character and was said to "follow the colon." It occasionally radiated through to the back and was partially relieved by antacids; it gradually became more severe. For one month prior to his second admission to the Barnes Hospital he had had increasing fatigue, especially at the end of the day, but he denied weight loss, other gastrointestinal complaints or symptoms of cardiac or pulmonary disease. He entered the Barnes Hospital on August 31, 1950.

Physical examination revealed his temperature to be 37°c., pulse 76, respirations 24 and blood pressure 115/68. The patient weighed 150 pounds. The significant findings included clubbing of the fingers and toes, palmar erythema, slight cyanosis and scant body and pubic hair. A few expiratory wheezes were heard over both lung fields. There was a draining sinus near the middle of the right costal margin, and the patient had had slight tenderness to deep palpation in the right upper quadrant. A ventral hernia was present. The right testicle was atrophied and there was a right varicocele. The prostate was slightly enlarged.

The laboratory data were as follows: red blood cell count, 4,330,000; hemoglobin, 14.3 gm.; white blood cell count, 5,550; differential, normal. Urinalysis, negative; urine bilirubin, negative; urine urobilinogen, 0.54 mg. per cent. Blood Kahn test, negative. Blood chemistry: non-protein nitrogen, 19 mg. per cent; fasting blood sugar, 79 mg. per cent; amylase, 107 units per cent; cephalin-cholesterol flocculation, 3+; thymol turbidity, 16.6 units; bromsulfalein retention, 25 per cent in thirty minutes, 12 per cent in sixty minutes. Roentgenogram of the chest revealed diffuse mottled densities throughout both lung fields, particularly marked at the bases; these changes were thought to suggest interstitial fibrosis. Gastrointestinal x-ray studies revealed esophageal varices, diverticulum of the duodenum and of the sigmoid colon and non-visualization of the gallbladder. X-ray examination after lipiodal injection of the sinus tract demonstrated no communication of the tract with the peritoneal cavity or the intestinal tract.

The patient was seen by a chest consultant who also suggested that the pulmonary changes visualized on the chest films constituted a form of interstitial fibrosis; he stated that he had seen similar changes in hemosiderosis.

About one week after entry the draining sinus was explored under local anesthesia. It was found to enter the abdominal cavity just below the eleventh rib and anterior to the termination of the twelfth rib. Dissection was carried down to what appeared to be the anterior surface of the liver and the tract was excised. A small cigarette drain was inserted. Five days after operation the sutures and drain were removed and all drainage ceased. At the same time the patient noted complete disappearance of the pain which had been present in that area. Microscopic examination of the excised tissue

showed only the changes of acute and chronic inflammation. There was no evidence of talc granuloma or of a foreign body. The patient was discharged on September 15, 1950.

Subsequent to discharge he felt almost entirely well and was able to return to work. He soon became depressed again, however, and began to eat poorly. About the middle of November, 1950, his epigastric pain returned and was more intense than ever. The patient described it as sharp and steady, and stated that it radiated straight through to his spine. It was more severe after meals and when he lay down, but it was not associated with nausea, vomiting, melena, jaundice, chills or fever. During the three months which elapsed between his second and final admissions to the Barnes Hospital, the patient lost 15 pounds and required codeine for relief of pain. He was admitted to the Surgical Service on December 9, 1950.

Physical examination revealed his temperature to be 36.5°C., pulse 80, respirations 16 and blood pressure 120/60. The general findings were as before except that cyanosis was not noted. Two examiners initially described a tender, ill-defined mass in the epigastrium and right upper quadrant. Subsequently, all examiners agreed that the mass was the liver and that the edge, which was sharp and at times very tender, extended 10 to 12 cm. below the costal margin.

The laboratory data were as follows: red blood cell count, 4,190,000; hemoglobin, 12 gm.; white blood cell count, 11,500; differential: eosinophils 1, stabs 10, segmented forms 71, lymphocytes 15, monocytes 3; the red blood cells and platelets appeared normal. Urine: negative except for 1+ proteinuria and a few hyaline and finely granular casts. Blood chemistry: total protein, 9.3 gm. per cent; albumin, 3.7 gm. per cent; globulin, 5.6 gm. per cent; amylase, 58 units; prothrombin time, 38 to 45 per cent of normal; cephalin-cholesterol flocculation, 3+; thymol turbidity, 14.5 units; bromsulphalein retention: 95 per cent in fifteen minutes, and 56 per cent in thirty minutes; total bilirubin, 1.08 mg. per cent; sodium bilirubinate, 0.3 mg. per cent; bilirubinglobin, 0.78 mg. per cent; cholesterol, 68 mg. per cent. Roentgenograms of the dorsal and lumbar spine showed only hypertrophic osteoarthritis.

During the first two weeks of his hospitalization an attempt was made to feed the patient a high carbohydrate, high protein diet, but he took it poorly and continued to lose weight. Several times he was found wandering about the corridor in a confused state. Codeine was found in his bedside table and the question of codeine addiction was raised; it was impossible to determine how much of the drug he had been taking. By December 22nd, approximately two weeks after entry, he was lethargic and weak. He had become moderately cyanotic and had developed dullness and rales at both lung bases. The heart was questionably enlarged to the left. There was a slight decrease in the size of the liver but signs of ascites appeared. The patient was transferred to the Medical Service.

On the night of transfer he became very agitated and was given 15 cc. of paraldehyde. His respiratory movements became shallow and the rate rose to between 28 to 44 per minute. Cyanosis increased. Intranasal oxygen therapy was instituted and the patient was given parenteral fluids. On the following day the red blood cell count was found to be 3,810,000, the hemoglobin, 14 gm., and the white blood cell count 19,500; the differential was similar to that recorded on entry. Additional data were as follows: non-protein nitrogen, 39 mg. per cent; blood sugar, 150 mg. per cent; chloride, 101 mEq./L.; carbon dioxide combining power, 24.6 mEq./L., alkaline phosphatase, 7 Bodansky units; total protein, 10.5 gm. per cent; albumin, 2.5 gm. per cent; globulin, 8.0 gm. per cent; urine bilirubin, negative. A chest x-ray showed elevation of the diaphragms, right pleural effusion and dense mottling above the right leaf of the diaphragm, thought to represent an area of pneumonitis. The patient's temperature, which had been normal, rose to 38.6°C., and he was started on 100,000 units of penicillin and 0.5 gm. of streptomycin every six hours; in addition, he was given intravenous fluids and large amounts of parenteral vitamins.

At 6 A.M. December 24th, two days after transfer to the Medical Service, the patient passed approximately 100 cc. of old blood per rectum. At that time his blood pressure was 80/60. Later that day he was found in shock after passing a brown-black stool in bed. He was given four blood transfusions, several units of plasma, vitamin K, adrenocortical extract and neosynephrine. An esophagogastric balloon was placed in the esophagus and inflated. At 1:30 A.M. on the following morning, December 25th, approximately 100 cc. of coffee-ground material were aspirated from the stomach. The patient

apparently improved transiently but he expired quietly four hours later.

CLINICAL DISCUSSION*

DR. CARL V. MOORE: This man first developed symptoms of his major disease in 1939 when he was fifty-five years of age. At that time, without any apparent prodromata, he suddenly vomited blood. Shortly thereafter he again had a hematemesis and entered a University Hospital where he was seen by the Professor of Medicine in that school. The diagnosis of Banti's syndrome was made and splenectomy and omentopexy were performed. Subsequently the patient's course was characterized by repeated hematemeses and abdominal pain, and it terminated in an episode suggestive of hepatic coma. It might be well to begin the discussion by focusing on the original diagnosis of Banti's syndrome. Since that diagnosis was made by an experienced, able internist, I am sure that it was justified on the evidence available at that time. Mr. Wheat, what is Banti's syndrome?

MR. MYRON W. WHEAT, JR.: There is considerable variation among different authorities in regard to their concept of Banti's syndrome, and it is difficult therefore to answer your question with any degree of definity. I believe, nonetheless, that it would be reasonable to assume that a patient with so-called Banti's syndrome would have splenomegaly of considerable degree, hypochromic microcytic anemia, leukopenia and, in all probability, cirrhosis of the liver. In retrospect, it would be difficult to defend the diagnosis of Banti's syndrome in this patient since he had ascites at the time he was first seen in 1939, and it is said that patients with Banti's disease with ascites die within one year or so.

DR. MOORE: You state that splenomegaly is a feature of Banti's syndrome, a statement with which I agree. What is the explanation for splenomegaly in this disease?

MR. WHEAT: The mechanism is not completely defined although it is thought in some quarters to be due to increased portal pressure.

DR. MOORE: Do you agree, Mrs. Thomasson, that the splenomegaly of Banti's syndrome is most likely congestive in origin?

MRS. MARY W. THOMASSON: Yes, I do.

DR. MOORE: Where is the lesion which produces the splenomegaly? Must it be in the liver itself. In other words, is cirrhosis a prerequisite?

MRS. THOMASSON: No. Splenomegaly may also arise on the basis of involvement of the splenic vein.

DR. MOORE: What sort of involvement?

MRS. THOMASSON: Thrombosis is a common cause.

DR. MOORE: Yes, splenic vein thrombosis may give rise to congestive splenomegaly; so may portal vein thrombosis. What other changes may occur in the splenic and portal veins, in addition to thrombosis, which may lead to portal hypertension?

MRS. THOMASSON: Usually there is considerable fibrosis around the vessels.

DR. MOORE: Yes, fibrosis is common, and cavernous degeneration also occurs. Does any of the information in the history help us to localize the site of the original vascular involvement?

MR. JAMES B. CUNNINGHAM: If the patient had had thrombosis or fibrosis of the splenic vein alone, I do not believe that the subsequent hematemeses that he suffered would have occurred, since removal of the spleen and the affected portion of the splenic vein usually is curative.

DR. MOORE: In other words, you believe that the patient had to have involvement of the liver or of the portal vein in order to have developed as much difficulty as he subsequently did.

MR. CUNNINGHAM: Yes, I think so.

MRS. THOMASSON: Isn't it conceivable that the entire process arose as a result of chronic gallbladder disease?

DR. MOORE: When the patient was explored in 1945, the gallbladder could not be identified because of the dense adhesions.

MRS. THOMASSON: Those adhesions may have been due to the omentopexy performed in 1939. At that time the omentum was presumably fixed to the abdominal wall; but had the patient had chronic gallbladder disease with rupture, it might be easier also to explain the subsequent sinus tracts which were found.

DR. MOORE: Do you believe that adhesions and fibrosis, secondary to rupture of the gallbladder, may have obstructed the portal vein and given rise to the entire disease picture?

MRS. THOMASSON: I think that explanation is worth considering.

DR. MOORE: Have you ever seen such a case?

MRS. THOMASSON: No, I have not, but I believe such cases have been reported.

* It should be noted that this clinico-pathologic conference differs from those usually published in the Journal in that the discussion was carried on by students from the Senior class rather than by members of the faculty.

DR. MOORE: Let's vary the procedure a little and ask Dr. Dammin whether he thinks fibrous tissue originating about a diseased gallbladder might actually give rise to portal obstruction, either partial or total.

DR. GUSTAVE J. DAMMIN: While looking for the cause of cavernous transformation of the portal and splenic veins, Dr. Klemperer reviewed all the cases reported up to a few years ago.[1] In many of those he studied there was a history of peritonitis, occasionally with gallbladder disease. Certainly in some instances of cavernous transformation of the portal system there is a history of inflammatory involvement in the liver and gallbladder region.

DR. MOORE: Mr. Weaver, we now have a number of suggestions, namely, that splenomegaly may have been due to cirrhosis or to a lesion in the portal vein. It is suggested that the latter may have arisen on the basis of thrombosis *per se*, or as a result of a fibrous tissue reaction secondary to disease of the gallbladder. Which of the two primary possibilities seems more likely to you?

MR. WILLIAM C. WEAVER: The patient's cirrhosis advanced very slowly for a number of years. I therefore would think of some other primary lesion.

DR. MOORE: Do you agree with that, Mr. Mason?

MR. JAMES C. MASON: No, I believe that cirrhosis was probably more important than Weaver suggests. First, although the patient does not have an alcoholic history, he has, as it were, an "alcoholic personality," and it may be that the history of alcoholism was not elicited. Second, necrosis within the liver may have increased the degree of splenomegaly. Finally, I believe the length of course, the absence of jaundice and the entire clinical picture can best be explained on the basis of cirrhosis.

DR. MOORE: You are not surprised then that cirrhosis might have a course of eleven or twelve years, without jaundice at any time, and nonetheless cause the death of the patient.

MR. J. C. MASON: According to a review by Ratnoff and Patek published in 1942,[2] 67 per cent of patients with cirrhosis have jaundice at one time or another. That leaves a rather large percentage who do not have it.

DR. MOORE: In Dr. Patek's series how many of the patients had a course lasting twelve years?

MR. J. C. MASON: Not very many but I do not believe that a course of that duration is beyond the limits of possibility.

MISS KATHRYN M. DEFLER: I have some specific figures; in all cases of portal hypertension 85 to 95 per cent of the patients have or develop cirrhosis of the liver. On a statistical basis, therefore, cirrhosis is a very good bet in this case.

DR. MOORE: Would you consider cirrhosis of the liver the most likely cause of the original congestive splenomegaly.

MISS DEFLER: Yes, I would.

MR. CUNNINGHAM: It should also be pointed out that in cirrhosis scarring may be fairly well localized around the portal vein; at the time of the first laparotomy for splenectomy, therefore, the liver may have appeared relatively normal grossly.

DR. MOORE: I believe we can summarize this phase of the discussion by saying that there is no unanimity of opinion regarding the nature of the primary disease. I am sure that if we assembled a group of physicians whose chief interest was liver disease, there would still be the same differences of opinion, one group holding that this patient had cirrhosis from the beginning and the other group believing that the patient probably started with involvement of the portal vein.

I believe it would be well to go on now to a consideration of the recurring abdominal pain which this patient experienced, and see if we can determine the nature of that complaint. The x-ray films are not particularly helpful, but I would like to make additional comments about the pain. First, it was present before the 1945 operation following which the fistula developed. Second, the patient stated that following the operation and the development of the fistula, the pain was often more severe when the sinus tract was not draining and tended to regress when the tract was open. Nonetheless, even at times when the sinus tract was draining freely he still had pain, and after the tract was excised the pain reappeared. Mr. Tyler, do you want to suggest an explanation for this pain?

MR. H. RICHARD TYLER: I can not give a single, specific answer, but I can list several possibilities. The pain may have arisen on the

[1] KLEMPERER, P. Cavernomatous transformation of the portal vein. *Arch. Path.*, 6: 353, 1928.

[2] RATNOFF, O. D. and PATEK, A. J., JR. The natural history of Laennec's cirrhosis of the liver. *Medicine*, 21: 207, 1942.

basis of gallbladder disease. The fact that the gallbladder was not found does not mean that it could not have been the site of disease. It could have been associated with the duodenal diverticulum; at least it seems to fit Bockus's description of the pain associated with duodenal diverticulas fairly well. Still another possibility is that the pain may have been due to cirrhosis. Cirrhotics at times do experience abdominal discomfort. Finally, it may have been due to a malignant neoplasm.

DR. MOORE: Do you think it is conceivable that this patient had malignant disease over a nine-year period? He first entered the hospital because of abdominal pain in 1942.

MR. TYLER: Yes.

MR. PHILIP S. NORMAN: Another suggestion which I believe worth mentioning, since the liver biopsy taken at the time of operation showed chronic periportal hepatitis, is that the pain may have been due to chronic recurring viral hepatitis. It has been described in that disease and patients have actually been explored because the occurrence of pain in chronic hepatitis was not appreciated.

DR. MOORE: Your suggestion is a good one; periportal hepatitis may indeed result from chronic recurring viral hepatitis. Mr. Weltge, do you believe there might be an association between diverticulum of the duodenum and possible gallbladder disease?

MR. WILFRED H. WELTGE: I do not see much relation between the two. It should be mentioned, however, that 75 per cent of duodenal diverticulas visualized by x-ray give rise to clinical symptoms. Therefore, duodenal diverticulum must be considered as a cause of the pain here.

MR. TYLER: Isn't it conceivable that the diverticulum may have been due to an adhesion?

DR. MOORE: Yes, it would seem to me that one must consider the possibility that the diverticulum arose as a result of adhesions between the gallbladder and the duodenum. Would anyone like to suggest the order of probability of the various explanations which have been proposed for the patient's pain?

MR. J. C. MASON: I would like to make one other suggestion to add to the confusion, namely, that the patient may have had pancreatic disease. Chronic pancreatitis is brought to mind by the fact that the pain radiated through to the back.

MR. NORMAN: In that regard, it should be mentioned that chronic pancreatitis often accompanies chronic hepatitis.

DR. MOORE: It is clear, I think, that the abdominal pain constituted a most difficult diagnostic problem for the clinicians who took care of this man; they were never able to establish its cause. Miss Defler, do you believe that there is any important relationship between the general illness from which this patient suffered and the development of the sinus tract? Or do you think that was just incidental to the operation; e.g., a wound abscess?

MISS DEFLER: It has already been mentioned that cholecystitis with rupture of the gallbladder and development of an abscess could have given rise to the tract. On the other hand, as you have suggested, wound infection with a chronic draining sinus also should be considered. If this patient did have chronic hepatic disease, he would probably have been more susceptible to wound infection than a patient with normal liver function. I think the sinus tract was incidental rather than of primary significance.

DR. MOORE: Still another problem in this case was the nature of the pulmonary lesion. Dr. Stearns, would you comment on the x-ray findings?

DR. COLBY S. STEARNS: At the time of the patient's second admission in September, 1950, the chest film was not remarkable except for the dense mottling at the bases which brought to mind the possibility of interstitial fibrosis. I think it is fair to say, however, that the findings were not especially unusual for a patient in this age group and that the interstitial fibrosis was not particularly marked. When he returned for the final admission, the chest x-ray findings were entirely different. The diaphragm was markedly elevated, and there was dense mottling above the right leaf which presumably lay posterior and was thought to be pneumonitis involving the right lower lobe.

DR. MOORE: In this regard, we might recall that the patient had clubbed fingers. I reviewed all of the records and was unable to determine to my own satisfaction how long clubbing had been present, but he probably had it for at least eight or ten years. In addition, cyanosis was described as far back as 1942. Miss Van Prooyen, would you comment on these findings?

MISS CORNELIA M. VAN PROOYEN: In one series of 300 cases of cirrhosis there were nineteen instances of cyanosis, which after thorough study were considered to have arisen purely on the

basis of cirrhosis. Clubbing of the fingers, of course, is not uncommon in liver disease. Even if the cyanosis and clubbing were due to cirrhosis, I would not be able to explain the interstitial fibrosis on that basis.

DR. MOORE: Dr. Stearns, how often do the radiologists make a diagnosis of interstitial fibrosis as was made in this case?

DR. STEARNS: I would say that we make it rather frequently in the older age group, and often make the qualifying remark that we believe it to be compatible with advancing age.

DR. MOORE: That information is important. When Dr. Alfred Goldman saw this patient in consultation, as is recorded in the protocol, he said that he had seen similar pulmonary findings in patients with hemosiderosis. Mr. Wheat, there seems to be no good reason for this man to have developed hemosiderosis but do you believe that hemochromatosis needs serious consideration here? It should be mentioned that on a number of occasions the patient's urine was said to have shown 1 to 2+ glycosuria. As far as I could determine, however, the glycosuria was always related to the infusion of glucose solutions, and therefore I did not include the information in the protocol.

MR. WHEAT: No, I do not.

MR. CUNNINGHAM: Of interest in regard to hemochromatosis is the fact that prior to the introduction of insulin, patients with hemochromatosis died not of liver disease but of diabetes mellitus. As well as I can determine, patients who now develop serious liver disease as a result of hemochromatosis do so because their diabetes can be adequately controlled by insulin and they are able to survive long enough to acquire cirrhosis. In this particular case, therefore, the absence of diabetes would be very much against hemochromatosis.

MR. WHEAT: An additional point is that patients with hemochromatosis usually have bronzing of the skin.

DR. MOORE: Does hemochromatosis ever occur in the absence of marked skin pigmentation?

MR. TYLER: It is stated that 10 to 20 per cent of patients with hemochromatosis do not exhibit abnormal pigmentation.

DR. MOORE: Returning to the question of the clubbing and the cyanosis, I gather that the general belief is that both may have been related to the liver disease. I personally would doubt that the cyanosis was. We are still left with no specific explanation for the interstitial fibrosis of the lung unless it was merely a concomitant of advancing age. Let us now consider the terminal episode, and see if we can explain the rather rapid downhill phase of the disease.

MR. PHILIP L. WAUGHTEL: One explanation for the terminal picture would be massive gastrointestinal bleeding.

DR. MOORE: That certainly is a possibility. Are there any others?

MR. J. C. MASON: Several of us were concerned with the marked enlargement and tenderness of the liver terminally, the marked globulinemia and the leukocytosis. As a tenable explanation we thought of carcinoma, either primary or secondary. Hepatomas are more common in cirrhotics than in patients without cirrhosis. If one postulates that this man had cirrhosis, a hepatoma is a distinct possibility. A second one is carcinoma of the pancreas with metastases to the liver. Further, in subacute hepatic necrosis, the globulin may be very high and the liver may enlarge terminally. Finally, all of us thought of Chiari's syndrome.

DR. MOORE: What is Chiari's syndrome?

MR. J. C. MASON: Chiari's syndrome is thrombosis of the hepatic vein which occurs rather often in cirrhosis and oddly enough somewhat more often in carcinoma of the liver. Had the hepatic vein thrombosed, the enlargement of the liver could be easily explained on that basis.

DR. MOORE: If the patient had subacute hepatic necrosis, on what basis did it arise?

MR. J. C. MASON: As a sequel to recurrent viral hepatitis.

MR. WAUGHTEL: I would like to enlarge on my statement attributing the terminal episode to gastrointestinal hemorrhage. I meant that as an explanation of death *per se:* I am sure that the patient had underlying severe progressive liver disease, possibly subacute hepatic necrosis going on to acute massive necrosis.

MR. J. C. MASON: In a recent paper in the New England Journal of Medicine[3] a case of infectious hepatitis followed by necrosis and marked hyperglobulinemia was described.

DR. MOORE: Do you favor that diagnosis here?

MR. J. C. MASON: No. I believe that carcinoma of the liver is more likely, even though

[3] ZIMMERMAN, H. J., HELLER, P. and HILL, R. P. Extreme hyperglobulinemia in subacute hepatic necrosis. *New England J. Med.*, 244: 245, 1951.

hyperglobulinemia is more common in subacute hepatic necrosis.

MR. TYLER: Hyperglobulinemia is certainly more common in chronic hepatitis than in cirrhosis. I was able to find only one case of cirrhosis with a globulin value above 8 gm. per cent, and that was in a patient who also had a hepatoma.

DR. MOORE: If this patient had subacute hepatic necrosis, what was the precipitating factor?

MR. TYLER: Probably either a recurrence of viral epidemic hepatitis or hepatic vein thrombosis. I would favor re-infection with the virus.

DR. MOORE: Mr. Mason, do you think the use of paraldehyde was detrimental to the patient?

MR. ARTHUR D. MASON, JR.: It may have been since to some extent it is detoxified in the liver.

MRS. THOMASSON: The question as to whether this patient was a codeine addict was raised. It is well known that morphine and its derivatives are not adequately detoxified in the presence of underlying liver disease; perhaps his ingestion of codeine was thus a factor in the terminal episode.

DR. MOORE: Morphine may indeed be detrimental under these circumstances, but what about codeine *per se?*

MRS. THOMASSON: I could find no specific reference to codeine in this regard.

DR. MOORE: We would all agree that paraldehyde may have precipitated the coma, but it was difficult to control the patient, and of all the drugs available paraldehyde may well have been the most innocuous.

MR. A. D. MASON: Hemorrhage also can precipitate hepatic coma. I believe that this patient's course would have been inevitably downhill, and I doubt that his course could have been significantly altered.

DR. MOORE: Mr. Norman, would you summarize your opinion about this case as a whole?

MR. NORMAN: I believe that the patient had portal hypertension on the basis of chronic liver disease. I would assume that the liver disease arose possibly from viral epidemic hepatitis with subsequent necrosis, scarring and finally cirrhosis, and that the patient may have suffered recurring attacks of viral hepatitis. I believe that the terminal episode was either acute or subacute hepatic necrosis, and that Dr. Dammin will show us a significant degree of recent necrosis in the liver.

DR. MOORE: You do not think the patient had a carcinoma?

MR. NORMAN: That is a good possibility, but it is not my first choice.

MR. J. C. MASON: In an editorial in the American Journal of Medicine,[4] Dr. Patek discussed the sequelae of viral epidemic hepatitis, and stated that patients with subacute hepatitis who developed the necrotic stage of the disease did not survive for a very long period of time. This patient had liver disease for many years. In the cholangiolitic form the patient almost invariably has jaundice which this patient did not have. I think the patient had Laennec's cirrhosis with carcinoma.

DR. MOORE: Are there any other comments?

MR. WHEAT: I would like to agree in general with Mason. I was impressed by the fact that when the patient came in on his second admission his liver was down about 3 cm., and at the time of his final admission it had come down 10 to 12 cm. below the costal margin. There are very few things which will cause enlargement of the liver to that degree within that period of time. Chiari's syndrome is certainly one of them and carcinoma is another. I should like to put, as my first choice, carcinoma of the pancreas with metastases to the liver.

MR. CUNNINGHAM: I should like to make two comments: First of all, for the sake of the record, it should be pointed out that if this patient had hepatic vein thrombosis, it was not truly Chiari's syndrome for that syndrome is idiopathic. When secondary, it should be called subendophlebitis of the hepatic vein. That is a technical point of course. Second, I would agree with Norman in that cases of chronic hepatitis described by Himsworth fit this clinical picture entirely.

DR. MOORE: In summary, this complicated case leaves us with many unexplained findings. The general consensus favors the fact that this patient had serious liver disease, possibly due to recurrent viral epidemic hepatitis with subacute necrosis terminally, or perhaps with cirrhosis upon which carcinoma, either primary or secondary, was superimposed.

Clinical Diagnoses: Cirrhosis of the liver with ? hepatoma or subacute necrosis.

PATHOLOGIC DISCUSSION

DR. RICHARD L. SWARM: There were 2,500 cc. of slightly blood tinged ascites in the peritoneal

[4] PATEK, A. J., JR. Relation of acute hepatitis to cirrhosis of the liver. *Am. J. Med.*, 8: 267, 1950.

cavity. The liver was of approximately normal size and shape with an irregular nodular surface. Bulging from the superior surface of the right lobe and along the inferior surface adjacent to the gallbladder bed and portal vessels were masses of soft gray tumor tissue. On section there was a marked increase in fibrous tissue which distorted the normal architectural pattern. In the superior portion of the right lobe there was a spherical mass of tumor 10 cm. in diameter, the central portion of which was soft and necrotic. Tumor from this mass invaded directly the adherent overlying diaphragm. In the liver there were also several smaller nodules about the large mass and at the hilum. The tumor invaded some intrahepatic veins and the portal vein at the hilum. Retroperitoneal, peripancreatic and porta hepatic lymph nodes were enlarged and fused together by metastatic tumor. In the region of the gallbladder bed and about the bile ducts, portal vein and hepatic artery there were extensive and solid fibrous adhesions through which were scattered small nodules of tumor. The cystic duct was completely occluded by a small pigmented ovoid gallstone. The gallbladder was thickened, reduced in volume, retracted and displaced inferiorly by the surrounding dense fibrosis. It and the cystic duct proximal to the point of obstruction contained only white mucoid material.

The splenic vessels terminated in fibrous adhesions in the region of the tail of the pancreas; the artery was patent, but the wall of the vein was irregularly thickened and its lumen markedly narrowed. The superior mesenteric vein was intact and not remarkable. On the pleural surfaces of the diaphragm there were gray nodules of tumor from 0.5 to 2.0 cm. in diameter, more on the right than on the left, which extended through the diaphragm. On the surface of the diaphragm and the lungs the subpleural lymphatics were prominent white linear streaks, and tumor was present in tracheobronchial lymph nodes. There was bilateral hydrothorax and the lungs were congested and partially atelectatic in the lower lobes. The veins of the hemorrhoidal plexus were dilated and thrombosed, as were also veins in the middle and lower third of the esophagus; however, no discrete point of bleeding was detected in the esophagus. There was an acute ulcer of the gastric mucosa 5 mm. in diameter on the lesser curvature, 10 cm. proximal to the pylorus, and 2,200 cc. of fluid and clotted blood were present in the stomach.

DR. GUSTAVE J. DAMMIN: The cirrhosis in this case was extensive and involved the liver in a uniform and diffuse manner which prompts us to call this diffuse nodular, or Laennec's, cirrhosis, although we recognize that it is sometimes difficult to distinguish between diffuse nodular cirrhosis and post-necrotic cirrhosis, occasional specimens showing features of both lesions. Slides from the biopsy of the liver performed in 1945 at St. Luke's Hospital revealed a pattern suggestive of diffuse nodular cirrhosis. In the microscopic field illustrated (Fig. 1) there is an increased amount of fibrous tissue containing a moderate number of lymphocytes. There is no evidence of active degeneration or neoplasia of the hepatic cells in these slides.

In the material obtained at autopsy six years after the biopsy (Fig. 2), the fibrous tissue is more compact and less cellular. There is some proliferation, or at least an apparently increased number, of small bile ducts in the connective tissue; and there is an active degenerative process going on in the hepatic cells. In Figure 3 there are two cells which clearly show cytoplasmic hyalin inclusions. These changes represent an early stage in a degenerative process, later transitional forms to complete necrosis being present in other parts of these sections.

Figure 4 shows the histologic appearance of the carcinoma described grossly. There is advanced anaplasia of these cells, and from their configuration it is easy to understand why the average duration of life is usually no more than three or four months once symptoms related to a primary carcinoma of the liver appear. The right upper corner of this illustration includes part of the portal vein, the lumen of which is occluded with thrombus and the wall invaded by tumor. In Figure 5 some of the highly anaplastic forms, tumor giant cells and mitotic figures, many of which were atypical, are shown. The general appearances of these cells are distortions of those of hepatic parenchymal cells, and there is nowhere any tendency toward the formation of bile ducts; we have therefore called this a hepatoma. The appearance of the tumor in the pleura where it was recognized grossly to permeate the pleural lymphatics is shown in Figure 6.

The nature of the types of involvement of the obstructed vessels at the porta hepatis is clarified by the section illustrated in Figure 7. The splenic

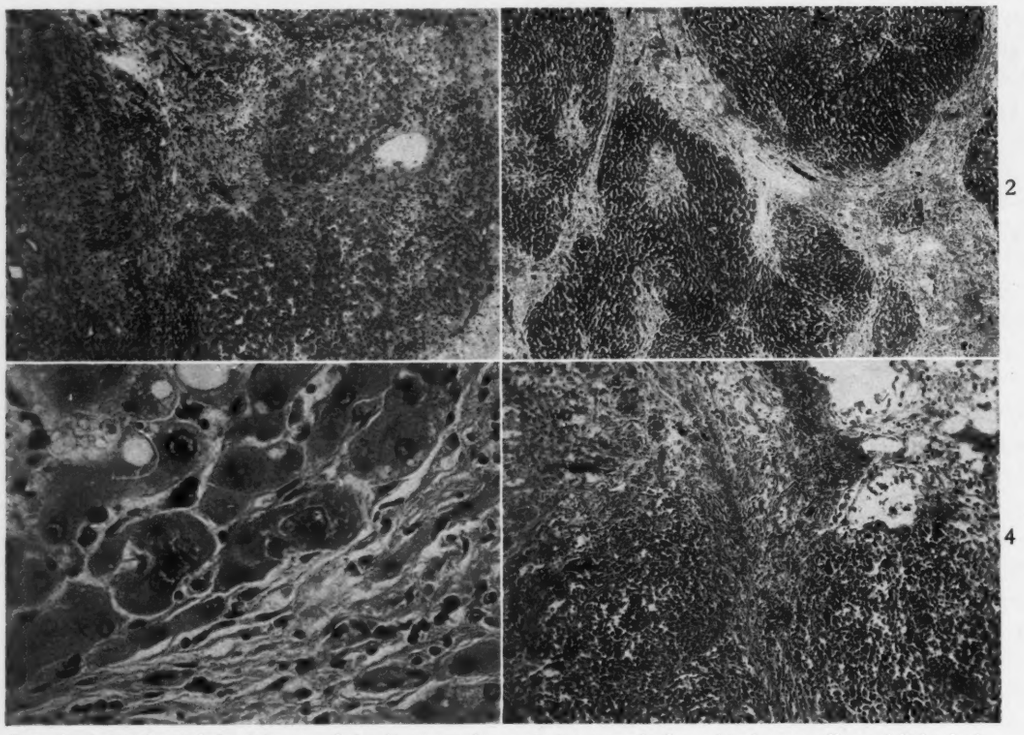

FIG. 1. A section of the biopsy of the liver performed six years before death; a well established cirrhosis of the diffuse nodular type is present.
FIG. 2. Diffuse nodular cirrhosis as it was present in the material obtained at autopsy.
FIG. 3. Cytoplasmic hyalin inclusions in hepatic cells at the time of autopsy; these are indicative of an active degeneration of the hepatic cells and transitional forms to complete necrosis could be found.
FIG. 4. Anaplastic liver cell type of carcinoma in the liver; in the right upper corner is the lumen of the portal vein which was filled with thrombus and tumor.

vein is represented by several small channels, none approximating the normal diameter of that vessel and some, like the one above the center of the figure, divided by a fibrous septum. Although there is fibrosis of the surrounding structures, there is no carcinoma in these vessels. The recent thrombus in the largest channel is continuous with that in the portal vein which at this level is filled with recent thrombus although in its more proximal portion it contained tumor. The lesion in the splenic vein is obviously older than those in the portal vein, and by both its gross and microscopic characteristics represents what has been described as cavernomatous transformation of that vessel.[1]

The final lesion illustrated (Fig. 8) is a dilated and thrombosed vein beneath the mucosa of the mid-portion of the esophagus; obviously this was a collateral channel that developed as a consequence of the portal hypertension and undoubtedly was casually related to the repeated episodes of hematemesis.

In reconstructing the sequence of events in this case, the nature of the cirrhosis remains somewhat doubtful. In any event, the history began with hematemesis eleven years before death followed shortly by discovery of an enlarged spleen. No evidence of involvement of the liver appeared for five years; then (1945) there was an episode that suggests hepatitis. The liver was discovered by biopsy to be already involved in a cirrhotic process of the diffuse nodular type. It is possible that this type of cirrhosis may represent the end stage of hepatic damage by any of several processes, one of which might be some form of hepatitis; however, as the splenomegaly antedates any evidence of involvement of the liver, it appears to have been related to the cavernomatous transformation of the splenic vein. It is recognized in such cases that a chronic inflammatory process can develop at the hilum of the liver either before or concommitantly with the changes in the splenic vein and result in portal hypertension. The fibrosis and contraction of the gallbladder is further evidence of such an inflammatory process, and we might suspect that acute cholecystitis with associated localized peritonitis

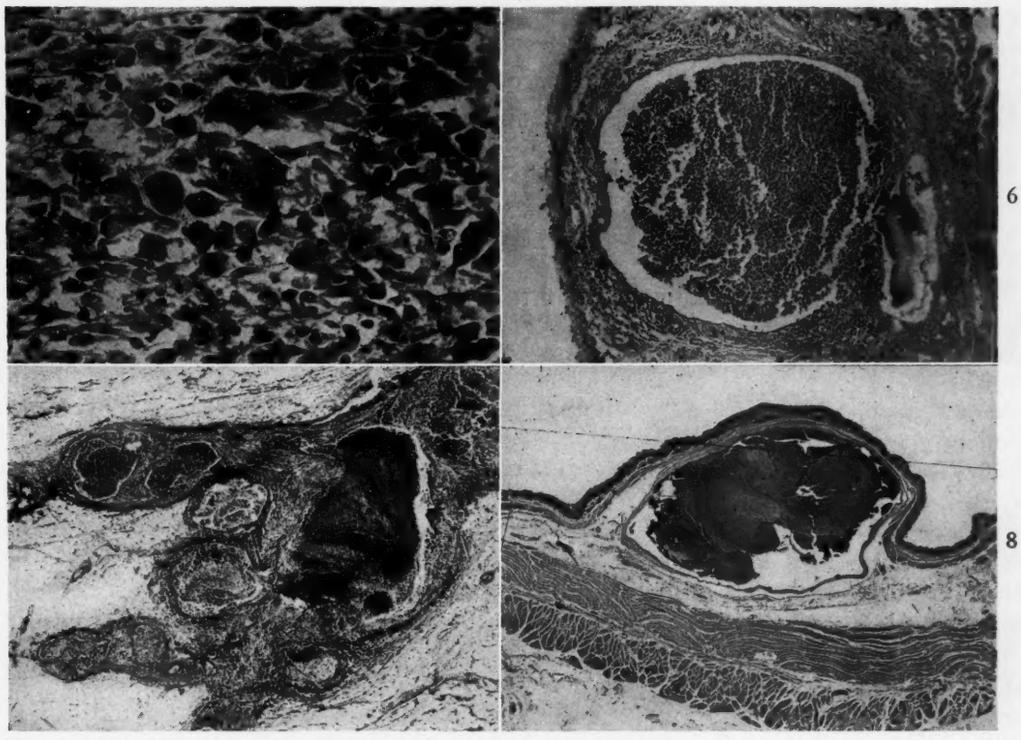

FIG. 5. Giant cells, mitotic figures and pleomorphism in the carcinoma which are indicative of marked anaplasia.
FIG. 6. A nodule of metastatic tumor in a subpleural lymphatic of the lower lobe of the right lung.
FIG. 7. Cavernomatous transformation of the splenic vein; note the numerous small channels, some of which are subdivided by septa, that have replaced the vein.
FIG. 8. A dilated and thrombosed vein in the mid-portion of the esophagus; a collateral vessel from the splanchnic circulation that was responsible for the repeated hematemesis.

could have involved the walls of the veins and led to the changes in the splenic vein. On the other hand, some authors have suggested that Banti's syndrome may follow hepatitis and a resulting post-necrotic cirrhosis which may be only severe enough to be manifest by portal hypertension, varices and splenomegaly which appear clinically as progressive features. Hepatitis bears no known relationship to cavernomatous transformation of veins, and to accept the possibility of an early unrecounted episode of hepatitis as the initiating lesion in this case would necessitate leaving that lesion uncorrelated.

The remainder of the lesions are less difficult to understand. The tumor is a liver cell type of primary carcinoma of the liver and consequently the more common type, being 3 to 5 times as frequent as the bile duct type. As occurs in 90 per cent of such tumors, it developed in a previously cirrhotic liver although the incidence of primary carcinoma of the liver is only about 3 per cent of all cases of cirrhosis. The short course after appearance of symptoms referable to the tumor is typical of most cases, but some may live longer as we have seen an instance of survival for more than two years after the tumor was proved by biopsy. In the other viscera old pleurisy, atelectasis and lymphatic permeation by tumor in the lower lobes of the lungs account for the radiographic findings relative to that organ; and the duodenal diverticulum was apparently a deformity due to invasion of that structure by the chronic fibrotic process that involved the gallbladder and the hilum of the liver.

Anatomic Diagnoses: Diffuse nodular cirrhosis; primary carcinoma of the liver, liver cell type; metastatic carcinoma in lymph nodes, diaphragm, lungs and the right adrenal; cavernomatous transformation of the splenic vein; esophageal varices; clotted and fluid blood in the stomach.

Acknowledgment: The photographs were made by the Department of Illustration, Washington University School of Medicine, St. Louis, Mo.

Case Reports

Diverticulosis of Jejunum with Hemorrhage*

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ACQUIRED diverticulosis of the small intestine is infrequent. By insufflating the small intestine in 300 consecutive necropsies Rosedale[1] found four cases of diverticula of the small intestine. Their infrequent recognition roentgenologically is emphasized by Case[2] who found them in only 0.1 per cent of 10,000 gastrointestinal x-ray studies.

Diverticula of the small intestine can cause serious bleeding. The first reported example was noted by Braithwaite[3] in 1923. Kozoll, McMahan and Kiely[4] have recently reported the seventh case. We will report herein two cases of diverticula of the jejunum with hemorrhage observed at the Emanuel Hospital, Portland, Oregon, during the past two years.

CASE I. C. W., a seventy-seven year old white female, was first admitted to the Emanuel Hospital October 24, 1948. For twenty-five years she had had recurrent episodes of lower abdominal cramping pain and diarrhea lasting a number of days. These attacks were usually brought on by dietary indiscretion or emotional disturbance. She had never been jaundiced. During the preceeding three years she had precordial distress on effort but was able to be reasonably active. She had led a full and vigorous life and had borne five children.

On physical examination her appearance was normal. The blood pressure was 148/68. Geographic tongue was present. The heart was not enlarged; its rhythm was regular and the rate rapid. A low-pitched systolic murmur was heard at the apex, referred to the left. A high-pitched systolic murmur was detected at the aortic area. No thrills were felt. The abdomen was tender across its lower half. No masses were felt. Neither the spleen nor liver was palpable. The laboratory examination revealed the blood count to be normal. The sedimentation rate was 107 mm. in forty-five minutes (Westergren). Examination of the urine was negative. The serology was negative. The impression was (1) arteriosclerotic heart disease with chronic aortic and mitral valvulitis and (2) irritable colon—as a cause for the abdominal distress.

During the succeeding few days the patient's abdominal distress became worse and extended to the right upper quadrant of the abdomen where considerable tenderness was found. Her temperature became elevated to 101°F. and the white blood cells increased to 14,500. Cholecystitis was present. The possibility of empyema was suspected. The patient's heart weakened and signs of left ventricular failure became apparent. The blood urea nitrogen was 31 mg. per cent. Despite the patient's poor condition she was explored on October 24, 1948. At operation performed by one of us (C. W. B.) the entire right upper quadrant was found to be extensively involved with adhesions which connected the stomach, duodenum, liver, colon and anterior abdominal wall. The gallbladder was enlarged and contained 100 cc. of hemorrhagic, foul-smelling fluid and two fairly large, faceted stones. The gallbladder was drained and not removed. The patient recovered very slowly and was discharged on the twenty-first postoperative day.

In May, 1949, she began to have attacks of abdominal pain and black blood in her stool. The gastrointestinal tract was x-rayed by her physician who found only diverticula in the sigmoid colon. Sigmoidoscopic examination disclosed a polyp at the rectosigmoid junction. Her hemoglobin was 42 per cent and red blood cells 2,100,000. The anemia precipitated cardiac failure. It was thought that the polyp and diverticula of the colon were the cause of her bleeding. She was transfused; the bleeding stopped and she again became comfortable and left the hospital.

During the summer and fall of 1949 she was not well; she complained of gaseous distress and poor appetite. She lost 30 to 40 pounds in weight. Blood was present in her stool from time to time. Because her condition grew progressively worse, she was again explored on November 2, 1949.

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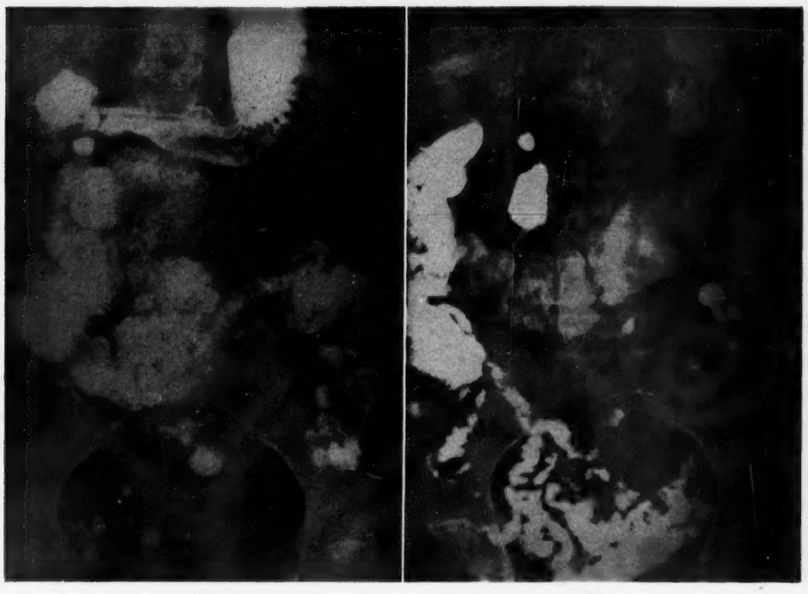


1A 1B

FIG. 1. Case I. A, Upper gastrointestinal x-ray showing jejunal diverticula; B, one-hour film again shows the diverticula.

At operation a diverticulum was noted at the rectosigmoid. The mesentery of the rectosigmoid was indurated. No tumor masses were felt in the colon. The colon was filled with a bluish content due to either ingested iron or blood. Two or three diverticula were palpated in the proximal jejunum. There was no bloody content in the small bowel and it was thought that the jejunal diverticula were not significant. Evidence of some hepatic cirrhosis was present. The spleen was somewhat enlarged. Since the chief findings pointed to the rectosigmoid as the seat of the trouble, a colostomy was performed bringing out the sigmoid. It was hoped that by having done this we might be able to differentiate bleeding at the rectosigmoid from that of the proximal colon.

The patient failed to improve and lost blood at intervals from the proximal loop. Transfusions were given to cover this loss. On December 27, 1949, another upper gastrointestinal x-ray was taken. At least two diverticula were visible arising from the duodenal loop. Also, a rather large diverticulum appeared to be arising from the proximal jejunum. It was then concluded that the jejunal diverticula were the source of bleeding from the upper abdomen. Accordingly on December 29, 1949, the abdomen was again opened. Many adhesions existed due to previous surgery and also due to the cholecystitis. Five or six large diverticula were identified in a proximal loop of jejunum. This loop was excised and the free ends anastomosed. No other intestinal pathologic condition was seen. The abdomen was closed. (Fig. 1.)

Pathologic examination of the specimen revealed it to be 26 cm. in length and moderately edematous. There were fourteen diverticula extending varying distances up to 2 cm. into the mesenteric attachment. The mucous membrane was intact. No area of ulceration, hemorrhage or neoplasia was seen. Microscopically no abnormality was seen. The postoperative course was marred by the development of an abscess in the gallbladder area. This was evacuated and the patient recovered. The bleeding stopped. Her blood count became normal and she was free from abdominal distress. On April 27, 1950, the colostomy was closed. The patient has since felt well and has been quite active for a woman of seventy-eight years.

Addendum: This woman remained free from intestinal bleeding for one year and one month after the jejunal diverticula were resected. She was then readmitted to Emanuel Hospital on January 19, 1951, because of recurrent melena. At this admission she was eighty years old and her hemoglobin was 40 per cent. She was given six whole blood transfusions of 500 cc. and on January 25, 1951, the large duodenal diverticulum was resected. The specimen showed no source of bleeding on pathologic study. She left the hospital February 13, 1951, with a hemoglobin of 75 per cent and was not bleeding. Unfortu-

nately, she was free from intestinal bleeding only two months and was again admitted April 13, 1951, with persistent melena and a hemoglobin of 40 to 50 per cent, even though twelve transfusions of 500 cc. each were given. She had received a total of forty-two transfusions of 500 cc. each during her various hospital visits.

She died May 14, 1951, and at autopsy no cause for the bleeding was found. The liver showed marked cirrhosis but no varices could be demonstrated in the gastrointestinal tract. The mucosa of the distal small bowel was hyperemic. All previous intestinal anastomosis were healed and in spite of many adhesions no loops were obstructed.

CASE II. F. S., fifty-seven year old housewife, was admitted to the Emanuel Hospital on April 4, 1948. She had been constipated ever since the birth of her children twenty-two years before. For the past three years every two or three days she had experienced cramping pains in the lower left quadrant of the abdomen and in the left groin, which would radiate across the lower abdomen. The cramps were intermittent but had no relation to meals and were associated with the passage of red blood in the stool. Nothing was found which would relieve the pain. The patient's condition had grown steadily worse during the past year. There was no change in her bowel habits. She grew weak and tired easily. There was no weight loss. Otherwise the history was irrelevant.

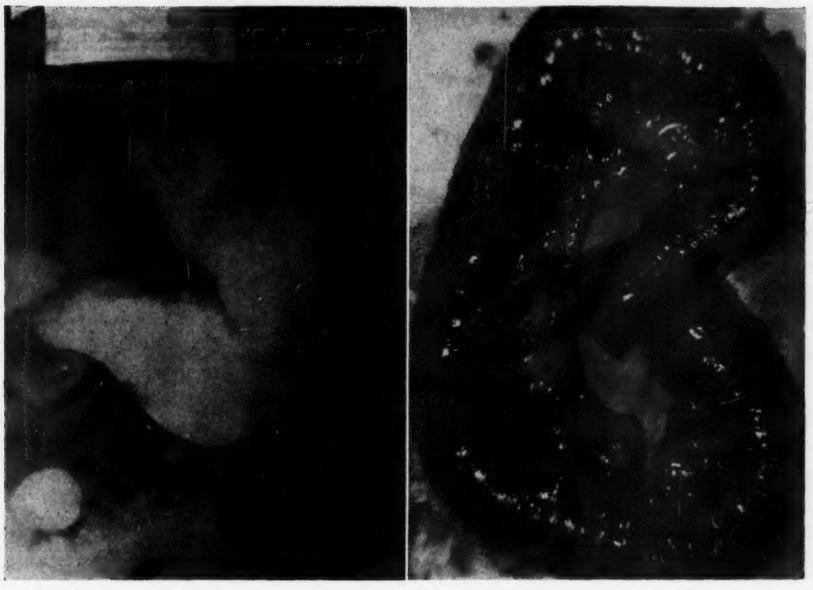
The patient was obese; she was 63 inches tall and weighed 178 pounds. Examination of the abdomen revealed moderate tenderness in the epigastrium and the lower left quadrant. No masses were palpable. Repeated proctosigmoidoscopic examinations were negative except on one occasion when black mucoid material was seen in the sigmoid.

Examination of the blood showed the hemoglobin to be 10.5 gm. (74 per cent); red blood cells, 3,700,000; white blood cells, 5,650; color index, 1.0; polymorphonuclears, 59 per cent; eosinophils, 2 per cent; small leukocytes, 36 per cent; monocytes, 3 per cent. The sedimentation rate was 37 mm. in forty-five minutes (Westergren). Urinalysis was normal except for four to five pus cells per high power field, occasional epithelium and a few mucus threads. The Kahn test was negative. Several stools were positive for blood following a meat-free diet.

X-ray examination October 30th showed the chest to be normal. Barium meal demonstrated a normal esophagus and a ptotic but filled stomach. The duodenal cap and the second and third portions of the duodenum were normal. Serial radiographs revealed no persisting defects in the stomach or cap. The films showed multiple diverticula in the distal duodenum and jejunum. There was also one small diverticulum on the duodenum adjacent to the ampulla of Vater. The barium meal showed normal progress at five hours. Five-hour films showed no unusual barium shadow in the upper abdomen which would indicate barium residue in the diverticula. At twenty-four hours the barium showed normal progress. A barium enema was given. The colon filled promptly. (Fig. 2.)

The cecum was slow to fill and was situated higher and more medial than usual. It was movable and not tender. The appendix was not seen. The distal ileum did not fill during the screen study. Radiographs of the colon demonstrated the atypical position of the cecum in a high and medial position thought to be due to a congenital anomaly of no clinical significance. There was a shadow just above the splenic flexure which suggested a slightly enlarged spleen. Several diverticula were present in the distal transverse colon and one or two small diverticula were seen arising from the sigmoid. Summary: (1) multiple diverticula of distal duodenum and jejunum, (2) diverticulum of duodenum, (3) diverticulosis of the colon, (4) possible slight enlargement of the spleen, (5) atypical position of cecum previously described.

It was believed that the jejunal diverticula were the source of this woman's trouble and accordingly a laparotomy was performed by one of us (C. W. B.) April 7, 1948. The following is taken from the operative report: The abdomen was opened through a left lower midline incision. The appendix had been removed. The large bowel was followed from the cecum completely around to the rectosigmoid. No evidence of growth was felt at any point. There were a few small diverticula in the sigmoid region. The gallbladder was normal except for a few adhesions between it and the duodenum. The stomach appeared and felt normal. The proximal jejunum was found to contain many thin-walled diverticula ranging in size from 4 cm. in diameter to that of about 0.5 cm. The process was present over a distance of about 80 cm. of the bowel. The involved area was resected and the vessels ligated individually with chromic



2 3

FIG. 2. Case II. Upper gastrointestinal x-ray showing "cannon ball-shaped" jejunal diverticula.

FIG. 3. Case II. Inflated resected portion of jejunum showing diverticula.

catgut, making the anastomosis without clamps. The cut ends of the bowel were oblique to increase the diameter of the opening. There was considerable redundancy of the jejunal mucosa but on completion the lumen would still admit a finger at the ring. The abdomen was closed without drainage. (Fig. 3.)

Pathologic examination was as follows: The specimen consisted of 80 cm. of small bowel and a moderate amount of attached mesentery. The external surface of this small bowel was smooth and revealed no indurated or ulcerated areas. At the mesenteric border there were at least twenty-two diverticula measuring up to 3 cm. in diameter. These revealed grossly no induration or external change. The attached mesentery contained numerous lymph nodes measuring up to 1 cm. in diameter. These nodes revealed no gross abnormality. On opening the bowel along its entire mesenteric border the mucosa was seen to be normal throughout except at the mesenteric region where the diverticula were located. Examination of the mucosa of these diverticula showed no abnormality. Microscopic examination demonstrated rather marked follicular hyperplasia of the lymphoid tissue. Diagnoses: (1) multiple diverticula of the small bowel and (2) marked follicular lymphadenitis.

Supplemental microscopic examination of the wall of the diverticulum revealed a mucosa covered by thin strands of muscle tissue. There was moderate accumulation of lymphocytes and a few eosinophils in the mucosa, and the epithelial cells were well preserved. There was no evidence of an active inflammatory process. Additional diagnosis: Diverticula of the ileum with the formation of enteric cystic structures.

The patient's recovery was uneventful. She was discharged on the nineteenth postoperative day, relieved of her symptoms.

COMMENTS

There are two types of diverticula of the intestine, congenital and acquired. When all layers of the intestine are present in its wall, a diverticulum is said to be a true diverticulum. An example of this is Meckel's diverticulum. The acquired diverticula are composed of mucous membrane supported by little or no smooth muscle. They may occur in any portion of the gastrointestinal tract, from the duodenum to the sigmoid colon. Their occurrence in the jejunum is rare. Edwards[5] found five cases in 881 autopsies during the past four years when particular search for the condition was made. This represented an incidence of 0.57 per cent.

Acquired diverticula usually occur in males, most of the cases being found in individuals past middle life. In Rankin and Martin's[6] fifty-two cases from the Mayo Clinic there were thirty-eight males; the average age of the group was

55.6 years and the age varied from twenty-one years to eighty-two years.

As Edwards[5] points out, the diverticula may be either single or multiple. The site of herniation corresponds with the site of entry of a blood vessel. The diverticula are typically located on the mesenteric border. In the case of a diverticulum on the antimesenteric border the opening is present at the site of entrance of an unusual vessel. There seems to be no question but that these diverticula are acquired. It is considered that two major factors are concerned in their production: First they are located at a site where the blood vessel leaves the mesentery and enters the bowel, offering a point of decreased resistance; the second factor is the increased intestinal pressure caused by irregular contractions of the small intestine.

Rankin and Martin[6] found that the majority of their patients gave no distinctive symptoms referable to the gastrointestinal tract. Others report vague abdominal pains and gas that may occur at varying intervals after mealtime. Relief of these symptoms after resection of the diseased bowel indicated the causal relationship. Bleeding occurred in about six per cent of the reported cases. In one case bleeding was severe, resulting in shock.[4] In most cases, however, bleeding was intermittent and not severe.

A diagnosis can be made only by keeping the entity in mind. Careful roentgenoscopic examination of the upper jejunum may disclose the characteristic balls of barium contained in the diverticula.

Treatment consists of surgical removal of the involved segment of jejunum. In one of our cases and in the experience of another[4] the true significance of the presence of jejunal diverticula was not recognized at the time of first operation. When bleeding continued postoperatively, the importance of the diverticula was appreciated. The involved segments were subsequently removed and recovery followed.

SUMMARY

1. Two cases of acquired diverticula of the jejunum associated with hemorrhage are reported. The diagnosis was made by x-ray preoperatively in both cases. Cure was effected by surgical removal of the involved segment. To date these two patients have remained symptom-free.

2. Diverticula of the jejunum are a possible cause of vague abdominal distress and gastrointestinal bleeding of unknown origin.

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Cardiac Failure after Aortic-pulmonary Anastomosis in Tetralogy of Fallot*

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THE operation described in 1945 by Blalock and Taussig[1] for the production of an aortic-pulmonary anastomosis and modified by Potts, Smith and Gibson[2] has been recognized as a great advance in cardiac surgery. A steadily mounting number of articles have appeared in the literature attesting to the marked improvement which occurs in these patients following this operation. Without the operation the immediate and future prognosis is poor. The operative procedure, however, adds an additional cardiac defect to those already present and the possibility of cardiac failure immediately presents itself. Recently Bahnson and Ziegler[3] described fifteen patients who died of congestive failure following the Blalock procedure. We recently observed an additional case.

CASE REPORT

A white male was thirty-one years old at the time he was first examined (W. K. G.). His parents and four younger siblings were healthy. The delivery was normal and the birth weight was 9 pounds. At the age of fifteen months cyanosis was noted by the mother. Physical incapacity increased when the patient began to walk, and shortly thereafter squatting was noted. Clubbing of the fingers was observed at about the age of seven years. The patient attended a cardiac school until the age of fourteen years at which time he was bedridden for ten weeks. A strong desire to be active compelled him to do light work when he was able. In a squatting position he was able to make his own bed. During the past two years epileptiform seizures occurred. The patient stated that swelling of the ankles had been noted since he was a boy.

When examined (W. K. G.) on January 26, 1949, the patient was undernourished and underdeveloped. His weight was 114 pounds and he was 67 inches tall. He was able to walk about 25 feet without dyspnea or squatting. Climbing on the examining table caused shortness of breath for several minutes. The face was markedly cyanotic as were the buccal mucous membranes. The tongue was thick and blue with protruding filiform papillae. The teeth were in poor condition. The conjunctivae were hyperemic. The digital nails were thickened and cyanotic with clubbing more marked in the fingers than in the toes. The heart rate was 90 per minute, with a pulse of small volume. The blood pressure was 130/75 in the arms and 160/90 in the legs. The apex beat was in the fifth intercostal space and the left border of the heart was in the mid-clavicular line. A short, harsh systolic murmur was heard best at the third and fourth intercostal spaces to the left of the sternum and no thrill was felt. Respirations were 28 per minute. The lungs were clear to percussion and auscultation. The abdomen was flat and soft with the liver edge palpable 2 cm. below the costal margin and without pulsation. Kidneys and spleen were not palpable. Good femoral pulsations were present. The genitalia were normally developed. Pitting edema of both ankles was present. The reflexes were physiologic.

Roentgen examination revealed the following: In the anteroposterior view the heart seemed of normal size and contour and did not have the characteristic boot shape of tetralogy seen in early life. No fullness was noted in the area of the pulmonary conus. The hilar markings were decreased and did not pulsate. Good right and left pulmonary arteries could be seen and the lung periphery was clear. The aortic shadow was increased.

In the right anterior oblique position there was a slight enlargement of the right ventricle. In the left anterior oblique view the pulmonary window was clear and the aorta again ap-

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peared to be enlarged. With fluoroscopy a left aortic arch was observed without auricular enlargement.

An electrocardiogram showed a sinus rhythm was present with normal P-R and QRS intervals. The P waves in leads II and III were peaked and inverted in CF_{IV}. The QRS complexes were deeply inverted in lead I and upright in III. The findings were compatible with right heart strain and cor pulmonale.

Laboratory data were as follows: Erythrocytes were 6.96 million per cu.mm. with a hemoglobin of 18.5 gm. and a hematocrit reading of 58.5 per cent. The corrected sedimentation rate was 11 mm. in one hour. The circulation time was twelve seconds and the venous pressure was 102 mm. The non-protein nitrogen was 39 mg. per cent.

The impression gained from the foregoing data was that of a tetralogy of Fallot, and due to the progressive deterioration in the patient's condition surgical procedures seemed to offer the only hope of survival. On September 21, 1949, the patient entered the Johns Hopkins Hospital where on September 26th a side-to-side anastomosis was made between the aorta and the left pulmonary artery. At the end of the operation the patient's condition was considered to be good. During the following twenty-four hours frequent emesis of large amounts of coffee ground material occurred. Whole blood was administered due to a rapid fall in the erythrocyte count. During the same day the patient had a generalized convulsion and became unconscious. On the second postoperative day the non-protein nitrogen had risen to 73. On October 1st a pericardial friction rub was heard and x-ray examination disclosed increased density in both upper lung fields. Aureomycin and penicillin were given. The liver margin was now three fingerbreadths below the costal margin but without pulsation. Edema of the lower extremities persisted. Frequent emesis occurred during the first two weeks following the operation and the friction rub could be heard until the third week. On October 12th a pericardicentesis was done but only 50 cc. of serosanguineous fluid was obtained which was sterile by culture. A gradual fall in the hemoglobin was noted with the red count finally reaching subnormal levels. By November 5th, however, the patient was much improved and left the hospital at his own request.

In the sixth postoperative week after the patient had returned home the clinical picture was different from that previously observed. The cyanosis had completely disappeared and the clubbing had subsided considerably, but the patient appeared to be anemic. Laboratory data on November 11, 1949, disclosed erythrocytes 3.04 million and hemoglobin 53 per cent. The white count and differential were normal. Marked anisocytosis and poikilocytosis were present. Urinalysis was normal except for the presence of a trace of albumin. The apex beat of the heart was now heard best over the sixth intercostal space and the left heart border extended into the left anterior axillary line. The right ventricle was also enlarged. A machine murmur was present in the second left intercostal space. The abdomen was distended and the liver enlarged to four fingerbreadths. Edema of the scrotum and lower extremities was present. Heart failure progressed in spite of maintenance of digitalis therapy.

On November 15th the urine was dark, the sclerae icteric and the appetite was becoming increasingly poor. Jaundice increased rapidly and the patient's condition deteriorated necessitating his final hospitalization. At this time the left heart border extended into the axilla. Harsh, prolonged grade IV systolic murmurs could be heard in all areas with a to-and-fro murmur over the second left interspace. The pulmonic second sound was greater than the aortic. The heart rate was 80 and the blood pressure 130/30, with positive capillary pulsation. On the left chest was a healed scar extending from anterior to posterior along the sixth intercostal space. Expansion was diminished bilaterally especially on the left and there was dullness over the lower two-thirds of the left lung field and over the lower one-third on the right. Marked ascites was present in the abdomen. Moderate clubbing of the fingers and toes was present. Edema remained as before.

An electrocardiogram disclosed sinus rhythm, right axis deviation and interventricular block. The T wave was depressed in lead I and inverted in II, III and CF_{IV}. The urine contained a large percentage of albumin but no cells or casts. The urinary chloride was 3 gm. per L. and a trace of bile was present. Non-protein nitrogen was 71 and the CO_2 combining power 49 volumes per cent.

The patient appeared in a critical condition and therapy was begun with oxygen, xanthines and mercuhydrin. Glucose and water intra-

venously were administered cautiously but had to be discontinued due to increasing pulmonary edema. The patient soon became comatose and expired twelve hours after admission.

Autopsy findings were as follows: The body of this young adult white male weighed 125 pounds. There was marked clubbing of the fingers and cyanosis of the fingertips; an old healed surgical scar of the left side of the thorax extended obliquely downward and forward from near the spine to 17 cm. below the nipple line, over-all 32 cm. long. The skin was markedly icteric. The peritoneum contained about 2 L. of a dark yellow clear fluid. The spleen was large, the lower edge 7 cm. below the costal margin, and the lower margin of the right lobe of the liver in the anterior axillary line was 5 cm. above the costal arch. The chest was long, flattened dorsoventrally. On the right side were about 850 cc. of a dark yellow limpid fluid with floating masses of fibrin. At the apex between the lung and the chest were small fibrous adhesions and medially there were others between the lung and pericardial sac. On the left side there were much more extensive adhesions between the lung and the parietal pleura; in several pockets formed by the adhesions there were approximately 850 cc. of limpid yellow fluid. Portions of the left lobe were compressed to the mediastinum and there were dense fibrous adhesions between the left lung and the pericardium. The pericardial sac was obliterated by edematous fibrous tissues. The heart was large. At the base it was 12 cm. wide and 7.5 cm. thick and the diagonal from the right auricular appendage to the left apex was 15 cm. The upper part of the spine was straight but in the lower thoracic and lumbar regions there was a wide S-shaped curvature. The thoracic duct had an outside diameter of 3 mm. At the lower level in the regions of the receptaculum chyli there were several large branches. The lining of the thoracic portion of the aorta was smooth. The abdominal portion had a few thin horizontal regions of fibrous tissue thickening.

At a level 1.5 cm. below the aortic end of the ductus botalli and on the front wall was an oval opening 1.2 cm. long and 8 mm. wide that communicated directly with the pulmonary artery. In the margins of this were fine black linen sutures. The lymph nodes around the trachea were moderately enlarged and blackened with carbon and there were several tortuous dilated veins on the right side behind the lymph nodes. The pulmonary veins had smooth linings stained yellow with bile. The pulmonary artery opened from behind had an inside circumference of 2.5 cm. The lining was smooth and the anastomosis mentioned with the aorta was with the terminal portion of the pulmonary artery 7 cm. above the leaflets and just before the left main branch. There was only a small vestige of eustachian valve, but a fenestrated membrane covering the region of the foramen ovale was 3 cm. long by 1.5 cm. At the upper edge was an oval opening with the diameter of 1.5 cm. Then there was a membrane of tissue 7 cm. wide and below a thin fenestrated tissue 1.3 by 1 cm. with six openings that ranged to 7 mm. diameter. When the root of the pulmonary artery was opened, the circumference of the ring under slight tension was 6.5 cm. The three leaflets of the valve were thin and had the usual structure and arrangement. Proximal to the pulmonic ring was a wide channel 3 cm. long and 2 cm. in circumference that represented the terminal portion of the conus arteriosus; this was separated from the right ventricle itself by a constricting fibrous ring with an opening 5 cm. in diameter. Along the margin of the fibrous ring were nodular deposits of lime that projected into the lumen 4 mm., and at the edge were small red granular tissues. The wall opposite the constriction was formed by myocardium and had a thickness of 4 mm. Behind and to the right just below the constricting ring was an oval opening 1.2 by 0.8 cm. which extended beneath a column carneae into a large interventricular defect of the septum to be described presently. The small right ventricle chamber from the constricting ring of the conus to the apex was 7 cm. long and from the tricuspid ring to the apex it was 6 cm. There was a fibrous tissue thickening and fusion of the leaflets of the tricuspid valve so that the ring did not fall away in a straight line. Measured along its free edge it was 9.5 cm. but the free margin was thickened by fibrous tissues. The chordae tendineae were short, some thin, others thickened by fibrous tissue, and they seemed to bind down the leaflets. The papillary muscles and columnae carneae were markedly hypertrophied. A large membranous thebesian valve was opposite the coronary sinus. The lining of the left auricle, the left auricular appendage and left ventricle was smooth but had a few grey fibrous thickenings. The interventricular septal defect was in front and behind the medial cusp of the tricuspid

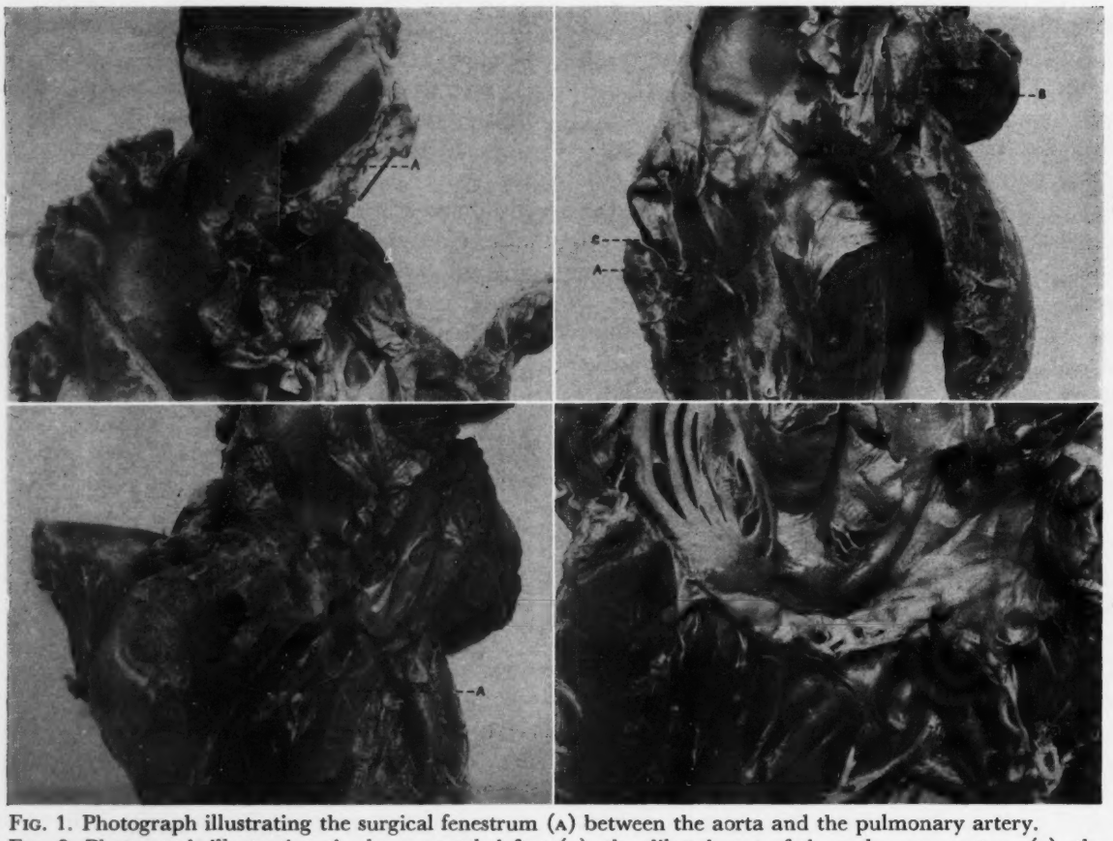

FIG. 1. Photograph illustrating the surgical fenestrum (A) between the aorta and the pulmonary artery.
FIG. 2. Photograph illustrating the large septal defect (A), the dilated root of the pulmonary artery (B), the calcified fibrous constriction of the pulmonary conus and (C) the anterior mitral leaflet, the aortic leaflets and the chronic fibrous pericarditis.
FIG. 3. Photograph illustrating the dilated root of the pulmonary artery, the calcified fibrous constriction of the pulmonary conus (A) and the fibrous pericarditis.
FIG. 4. Photograph illustrating the fibrous thickening of the tricuspid leaflets, the fenestrated tissues of the foramen ovale and the hypertrophied muscle tissues of the right ventricle.

valve. It was a large oval opening reaching upward behind the cusp about 3 cm. in its greatest diameter and it communicated, as mentioned, with the fenestrum just below the constriction in the pulmonary conus of the right ventricle. The chamber of the left ventricle was dilated. The papillary muscles were moderately thickened. The chordae tendineae were thin. The anterior mitral leaflet was thin and had the usual form, so also the posterior leaflet. The circumference of the mitral ring under slight tension was 7 cm. The length of the left ventricle from the mitral ring to the apex was 7 cm. The first portion of the pulmonary artery above the constriction was dilated and the wall included some muscle tissues like myocardium. The circumference here was about 5.5 cm. The length of the left ventricle from the attachment of the aortic leaflets to the apex was 8.5 cm. The circumference of the aortic ring under slight tension was 8.5 cm. The leaflets were thin except the nodes of Arantius that were slightly thickened by fibrous tissue. The root of the aorta beyond the aortic valve had an inside circumference of 6 cm.; distal to the anastomosis with the pulmonary artery the circumference was 4.8 cm. and in the mid-portion of the arch it was 5 cm. The mouth of each coronary artery was widely patent and in the usual position, each one 5 mm. in diameter. The septal defect mentioned was just below the aortic valve leaflets in the upper anterior portion of the septum. It had a rounded edge, was 3 cm. long and 3 cm. anteroposteriorly. It communicated freely with the right ventricle and also with the accessory opening mentioned in the conus of the pulmonary artery above the constricting ring. The myocardium of the left ventricle measured behind along the septum at the base was 2 cm. and toward the apex it was 1.5 cm. thick. Sur-

faces made by cutting the myocardium had brown fibrillar tissue stained with bile. The heart weighed 535 gm. (Figs. 1 to 4.)

Examination of the suprarenal glands, the kidneys, the ureters, the urinary bladder and other pelvic structures, the bile and pancreatic ducts, pancreas, the abdominal lymph nodes, testes and the neck structures disclosed no unusual changes. The spleen weighed 450 gm. It had two small healed infarcts and a chronic passive hyperemia. The liver weighed 1,275 gm. The capsule was finely granular. The tissues beneath were tan-brown mottled yellow and had lobular markings of chronic passive hyperemia.

The essential portions of the anatomic diagnosis were: large congenital interventricular septal defect of the heart; hypoplasia and calcified fibrous and verrucous constriction of the conus arteriosus of the heart; dilatation of the terminal portion of the conus arteriosus of the heart; hypoplasia of the right ventricle of the heart; widely patent and fenestrated membranous foramen ovale; surgical anastomosis and fenestrum between the pulmonary artery and thoracic portion of the aorta; bilateral chronic obliterative fibrous pleuritis; chronic fibrous endocarditis of the leaflets of the tricuspid valve and heart; hypertrophy of the myocardium of the right and left ventricles of the heart; dilated left ventricle of the heart; focal fibrous endocarditis of the right ventricle of the heart; marked clubbing and cyanosis of the fingertips; marked generalized icterus; bilateral hydrothorax; ascites; marked chronic passive hyperemia and fatty changes of the liver; chronic passive hyperemia and old infarcts of the spleen; anasarca.

COMMENTS

This case presents several interesting features from the standpoint of altered anatomy and physiology. In addition to the classical tetralogy as originally described by Sandifort in 1777[4] and later named for Fallot in 1888,[5] an auricular septal defect and an artificial ductus arteriosus were present. Miskall[6] described the case of a two and a half year old child that was born with these same defects. Uhley[7] states that the auricular defect adds considerably to the work of the right heart since the flow is from left to right due to the effect of gravity. Pulmonary stenosis adds further stress to the right heart and the cardiac reserve is reduced to a minimum.

When the idea was conceived of producing a patent ductus arteriosus to improve the pulmonary circulation, it was anticipated no doubt that in a certain percentage of the cases congestive failure would develop in addition to other complications.[8] It was hoped that by relieving anoxemia the cardiac reserve would be increased, however. In 1946 Blalock[9] reported that slight cardiac enlargement had been encountered but no cases of congestive failure. Potts and Gibson[10] pointed out that the basic pathophysiologic condition remains and that the creation of an artificial ductus arteriosus adds extra work to these hearts. These authors also noted cardiac enlargement but encountered no cases of congestive failure. Stephens[11] reported no cases of congestive failure in twenty-eight cases that followed the Blalock operation.

The presence of an arteriovenous communication has been shown to result in hypervolemia as a compensatory mechanism.[12,13] Warren et al.[14] studied over forty such cases and demonstrated a decrease in blood volume in one-third of the patients following closure of the A-V communication. Eppinger et al.[15] reported an increase in the blood volume following experimental production of a ductus in dogs and also found that the volume was reduced in human subjects following ligation of the ductus. They also state that the presence of a patent ductus may increase cardiac work by as much as 400 per cent. Studies on congenital heart disease[16] disclosed that hypervolemia was present in this group and bears a relation to the polycythemia which is present. Circulatory impairment results in a state of chronic anoxia (especially in the cyanotic types) and this in turn stimulates the bone marrow to increased red cell production resulting in polycythemia and hypervolemia. As a result the blood viscosity increases and cardiac reserve is further reduced.[17] Following operation all of these abnormalities correct themselves. Potts[18] has observed an average fall of two million cells in the erythrocyte count in a period of two weeks without jaundice or elevation of the icterus index. On the basis of the course and the autopsy findings it was believed that the marked jaundice present in our case was on the basis of hepatic changes secondary to chronic passive congestion. The possibility of superimposed viral hepatitis cannot be definitely excluded, however.

Rich[19] has pointed out that patients with pulmonary stenosis who died following operation always had pulmonary thrombi. Further in-

vestigation revealed that all patients with this condition developed this complication regardless of whether or not they were subjected to operation. Increased blood viscosity is believed to be the basis of this complication. Our patient also was found to have a few small pulmonary thrombi.

Bahnson and Ziegler,[3] as previously stated, have reported fifteen (3 per cent) fatal cases of congestive failure in 500 cases in which the Blalock procedure was performed. Five of these patients showed chronic passive congestion while the remainder died a few hours postoperatively of pulmonary edema. The time of survival varied from three to sixty-seven months following surgery.

The reason for the development of congestive failure in this case is not immediately apparent. The postoperative course was complicated by pleural effusion, pericarditis, azotemia, mild anemia and finally jaundice. The loss of the polycythemia, cyanosis and the return of the clubbed fingers toward normal would indicate that anoxia had been relieved by the operation. In spite of this, however, intractable congestive failure developed. The presence of an auricular septal defect together with the increased work load introduced by the patent ductus may have been all that was necessary to exhaust the remaining cardiac reserve.

SUMMARY

The case of a thirty-one year old white male presenting the tetralogy of Fallot with an interauricular defect is summarized. Surgical aortic-pulmonary arterial anastomosis was made. Death from congestive failure occurred three months following operation. The gross and microscopic tissue findings are described. Some of the mechanisms of altered physiology as related to the development of congestive failure are discussed.

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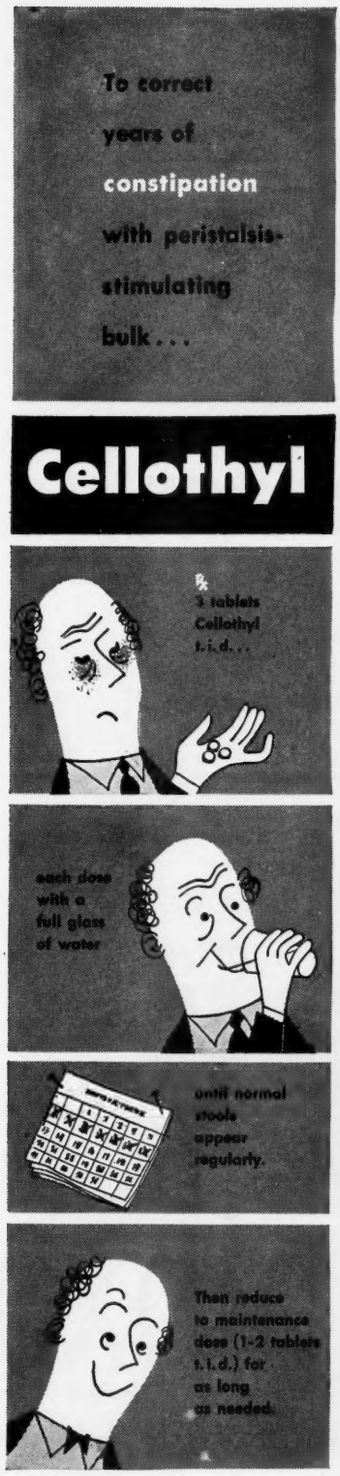

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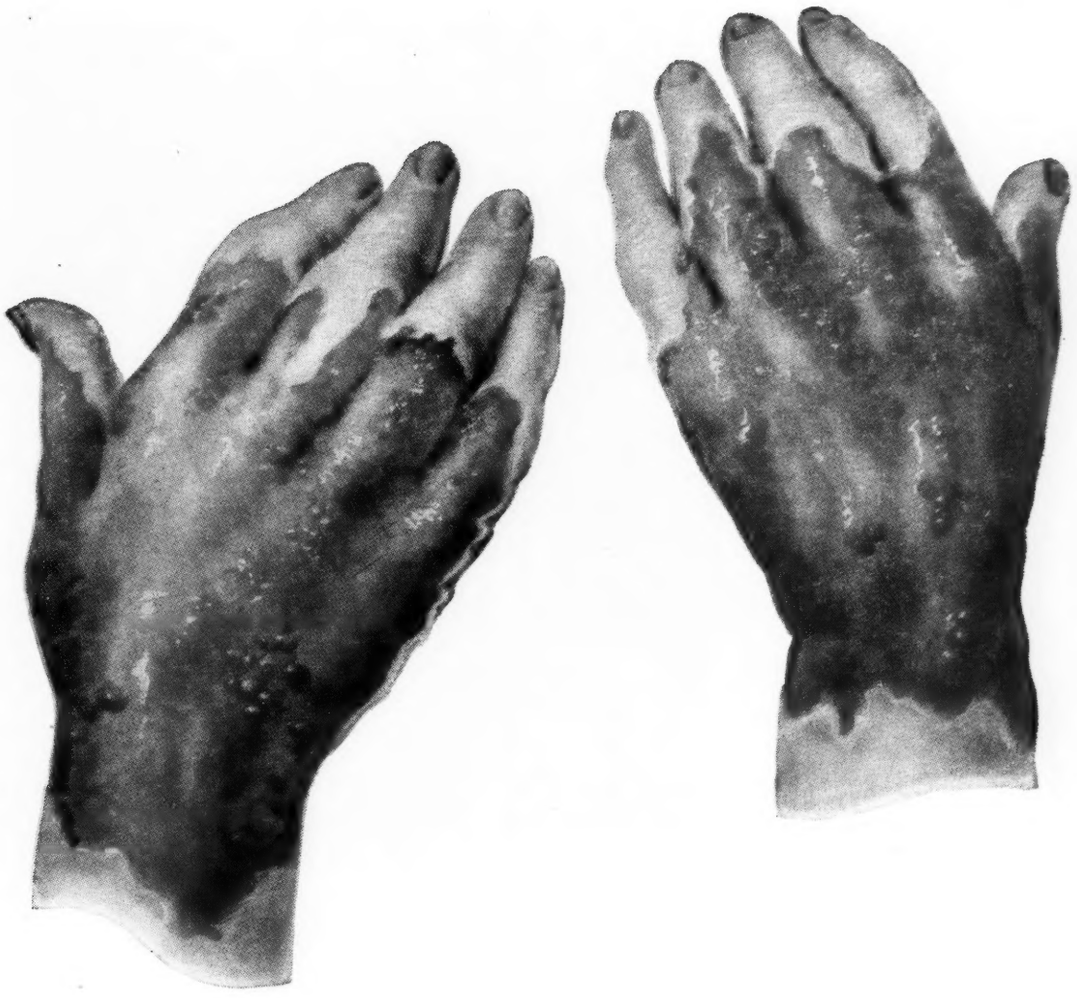

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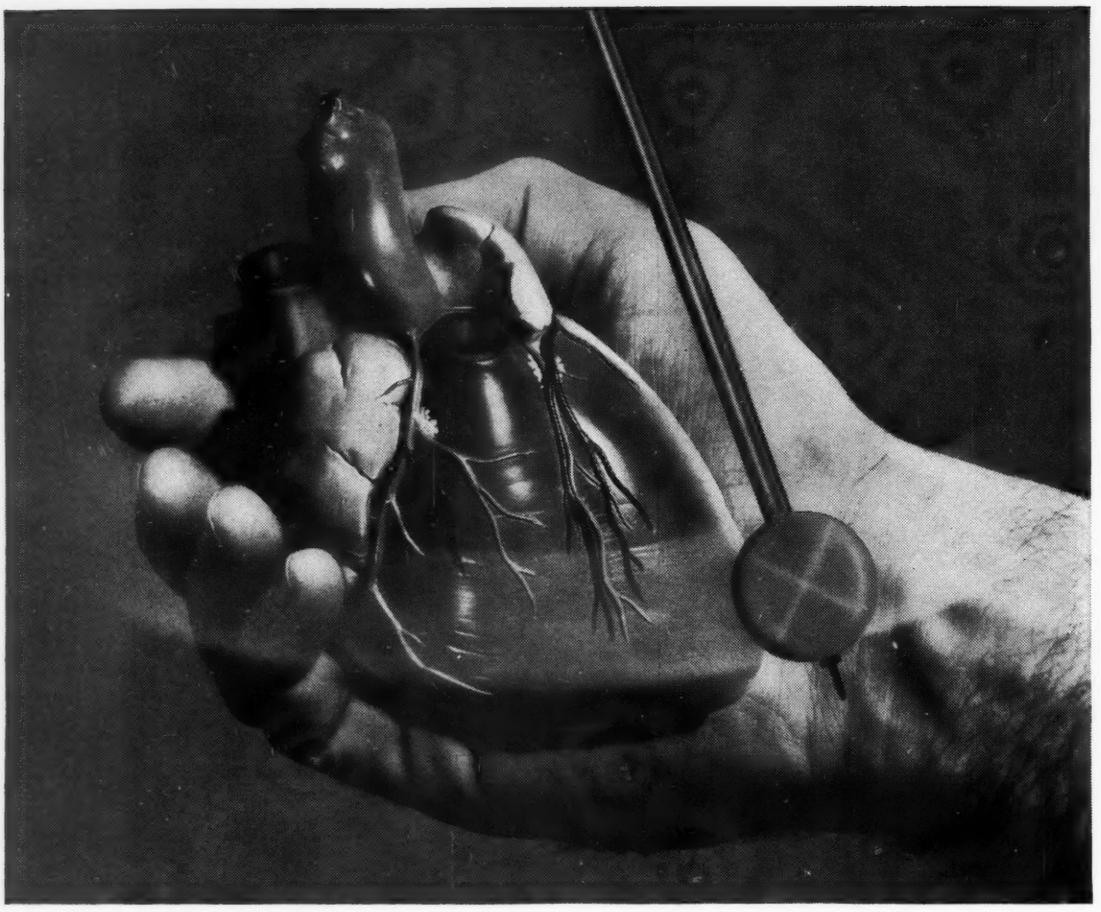

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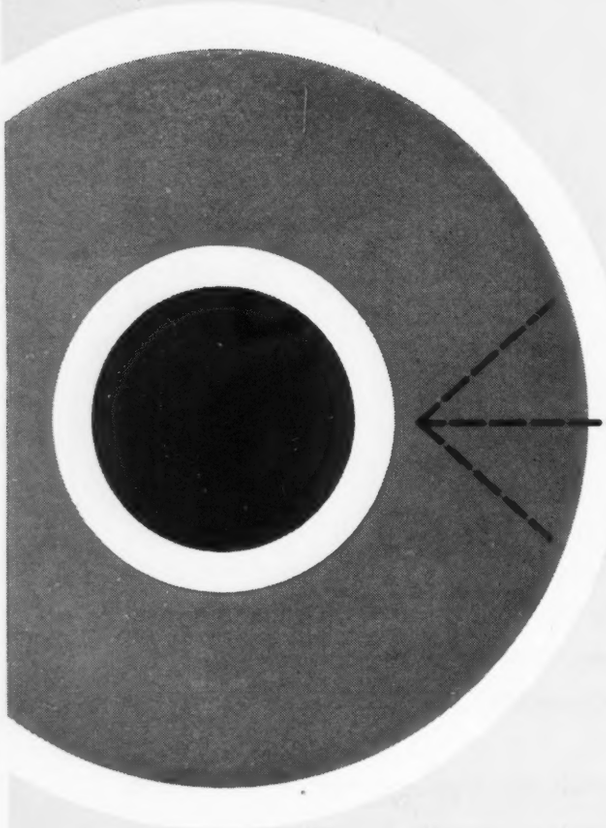

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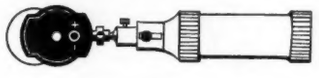
bacterial and rickettsial infections, as well as
certain protozoal and large viral diseases.

AUREOMYCIN

Hydrochloride Crystalline

Lederle

The Ophthalmologist now possesses in aureomycin a therapeutic agent effective against many infections of the eye, whether caused by bacteria or by large viruses. A half per cent solution is nonirritant to the conjunctiva, so that aureomycin may be given locally, systemically, or in both ways. It has been found of value in most types of conjunctivitis, as well as in dendritic keratitis and uveitis; and is of importance in the treatment of the acute stage of trachoma. Aureomycin is invaluable in both operative and nonoperative ophthalmology.



Packages

Capsules: Bottles of 25 and 100, 50 mg. each capsule. Bottles of 16 and 100, 250 mg. each capsule.
Ophthalmic: Vials of 25 mg. with dropper; solution prepared by adding 5 cc. of distilled water.

LEDERLE LABORATORIES DIVISION
AMERICAN Cyanamid COMPANY
30 Rockefeller Plaza, New York 20, N. Y.

for Control

in Sedation and Hypnosis...

Neuronidia®

(Elixir of diethylmalonylurea — Schieffelin)

Neuronidia is an effective sedative and hypnotic. It may be safely used in insomnia, hysteria, neurasthenia, thyroid diseases, chorea and mental disturbances. *Neuronidia* is indicated in virtually all cases of nervous disturbances uncomplicated by pain.

Pharmacological and clinical research have demonstrated that the depth and degree of sedation and hypnosis can be readily controlled with barbital, the active ingredient of

NEURONIDIA

Neuronidia contains per teaspoonful:
0.13 Gm. diethylmalonylurea

Dosage: Orally, as a sedative
½ to 1 teaspoonful repeated as indicated
As a hypnotic
2 teaspoonfuls before retiring

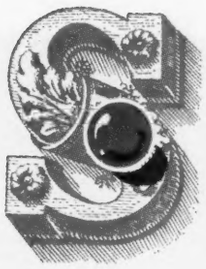
℞ Sodium salicylate ʒIV
Neuronidia ʒIV

Sig: *To induce sleep and produce analgesia*
one dessertspoonful at bedtime.
For sedation and analgesia
One teaspoonful two or three times daily as required.

Supplied: Bottles of 8 fluid ounces, and 1 gallon

Professional samples and literature are available on request.

Schieffelin & Co. since 1794 / *pharmaceutical and research laboratories*
24 Cooper Square, New York 3, N. Y.



ugar-coated for dependable diuresis

Sugar coating is one reason for the superiority of Tablets MERCUHYDRIN with Ascorbic Acid.

Maximum absorption of mercury occurs in the stomach and duodenum—too high for enteric-coated tablets. But poorly tolerated oral mercurials *must be* enteric-coated. Only well-tolerated Tablets MERCUHYDRIN with Ascorbic Acid can be sugar-coated . . . give consistently greater diuresis with less mercury.

For dependable diuresis and minimal side effects prescribe

tablets

MERCUHYDRIN®

with ascorbic acid

The simplest method of outpatient maintenance

dosage: One or two tablets daily, morning or evening, preferably after meals.

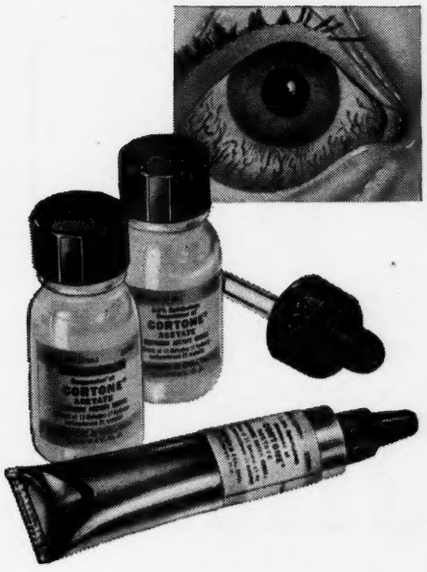
available: Bottles of 100 simple sugar-coated tablets each containing meralluride 60 mg. (equivalent to 19.5 mg. of mercury) and ascorbic acid 100 mg.

To secure the greatest efficacy and all the advantages of Tablets MERCUHYDRIN with Ascorbic Acid, prescribe a three-week initial supply . . . 25 to 50 tablets.

M-15

Lakeside Laboratories, INC., MILWAUKEE 1, WISCONSIN

Cortone®



now available in product forms for local use in eye diseases

Topical Administration

Preferred in inflammatory lesions of the anterior segment:

OPHTHALMIC SUSPENSION OF CORTONE® ACETATE
0.5%—5 cc. bottles
2.5%—5 cc. bottles
Choice of concentration is dependent on the severity of the inflammatory process. *Do not dilute or mix with other substances.*

OPHTHALMIC OINTMENT OF CORTONE® ACETATE
1.5%—3.5 Gm. tubes
Where use of an ointment is more convenient, *e. g.*, for application at bedtime.

Systemic Administration

CORTONE® tablets or the injectable suspension may be reserved for the treatment of diseases of the deeper ocular structures

It is gratifying to report at this time that increasing supplies of Cortone are being made available. We are continuing our efforts to accomplish a steady rise in production and to maintain equitable distribution.

Literature on Request

Cortone®

ACETATE

(CORTISONE Acetate Merck)

(11-Dehydro-17-hydroxycorticosterone-21-acetate)

MERCK & CO., INC.
Manufacturing Chemists
RAHWAY, NEW JERSEY
In Canada: MERCK & CO. Limited—Montreal

CORTONE is the registered trade-mark of Merck & Co., Inc. for its brand of cortisone.

When treating Urinary Tract Infections

consider

ACCEPTED
COUNCIL ON PHARMACY AND CHEMISTRY
AMERICAN MEDICAL ASSOCIATION

First

Because-

- It is quickly effective against the most common urinary pathogens.
- Organisms seldom, if ever, develop resistance to this drug.
- Supplementary acidification unnecessary (except where urea-splitting organisms such as *B. proteus* occur).
- It is exceptionally well tolerated—such complications as gastric upset, skin rashes, blood dyscrasias, or monilial overgrowth are unlikely to occur.
- No dietary or fluid restrictions are required; simply administer 3 or 4 tablets t.i.d.
- The comparatively low cost of MANDELAMINE* lessens the probability of complaints from patients about the high cost of medication.

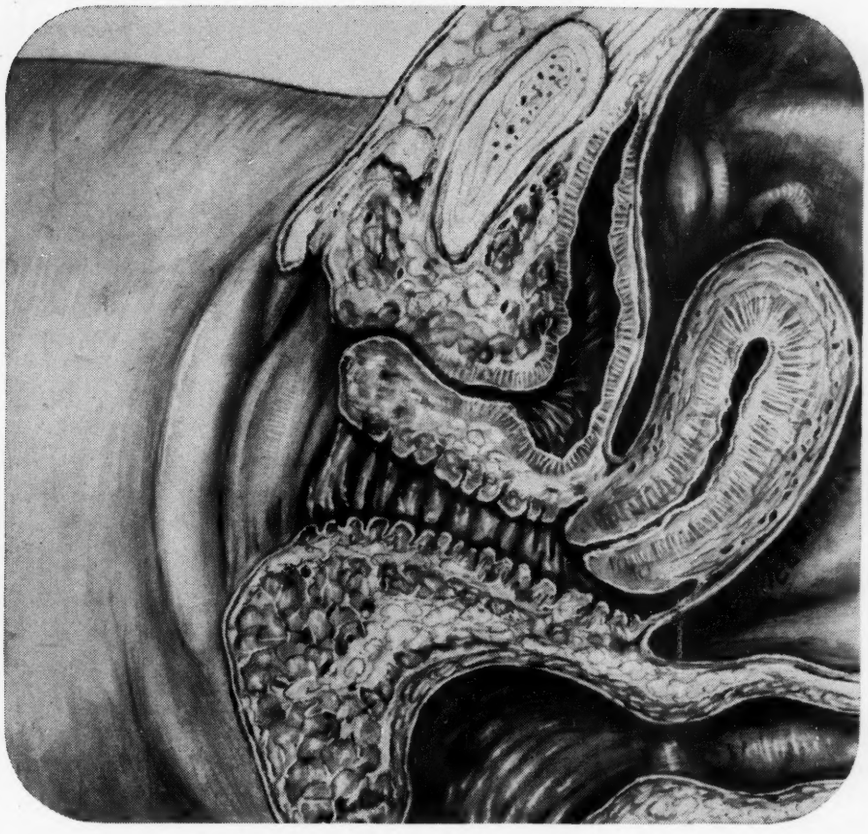
Suggested for use in the management of cystitis, pyelitis, pyelonephritis, prostatitis, nonspecific urethritis, and infections associated with neurogenic bladder and urinary calculi, as well as for pre- and postoperative prophylaxis in urologic surgery.

Supplied as enteric-coated tablets in bottles of 120, 500, and 1000. Complete literature and samples to physicians on request.

NEPERA

NEPERA CHEMICAL CO., INC.
Pharmaceutical Manufacturers
NEPERA PARK, YONKERS 2, N. Y.

*MANDELAMINE is the registered trademark of Nepera Chemical Co., Inc., for its brand of methenamine mandelate.



*"Trichomonas will not flourish in a normal vagina."**

FLORAQUIN®

NORMALIZING TREATMENT FOR VAGINITIS

The clinical success of Floraquin in the control of vaginal infections is based on its *twofold* action:

1 It serves as an effective trichomonacide and combats existent pathogenic organisms.

2 It stimulates restoration of a "normal vagina" by—
. . . replenishing normal mucosal cell glycogen
. . . stimulating restoration of normal epithelium
. . . restoring the normal vaginal pH favorable to the regrowth of normal *protective* flora.

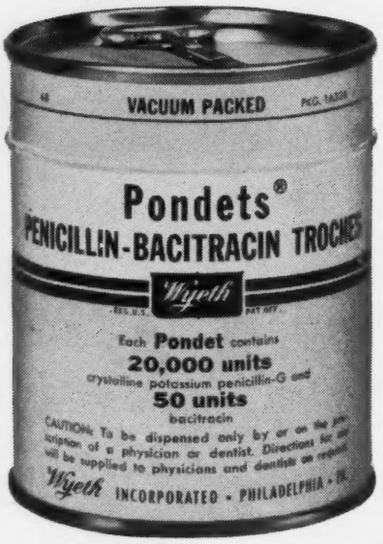
Floraquin combines the potent trichomoracide and fungicide, Diodoquin-Searle (diiodohydroxyquinoline), with lactose, dextrose and boric acid.

SEARLE

RESEARCH IN THE SERVICE OF MEDICINE

●

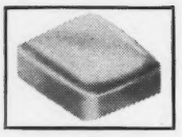
*Passmore, G. G.: Treatment of Discharges from the Vagina in Private Practice, North Carolina M. J. 11:487 (Sept.) 1950.



Wyeth®

PONDETS®

contain BOTH PENICILLIN and BACITRACIN



In a delicious hard candy base that completely masks antibiotic taste.

ADVANTAGES:

More potent antibiotic action

Penicillin and bacitracin exhibit true synergism.[1,2]

Wider antibacterial Spectrum

Organisms with little or "borderline" sensitivity to either antibiotic alone, are often readily susceptible to this combination.

Effective Oral Levels

Lasting at least one-half hour in most patients.

1. Eagle, H., and Fleischman, R.: Proc. Soc. Exper. Biol. & Med. *68*:415, 1948
2. Bachman, M. C.: J. Clin. Invest. *28*:864, 1949

In each troche: 20,000 units Crystalline Potassium Penicillin-G, and 50 units Bacitracin.

PONDETS®

PENICILLIN-BACITRACIN TROCHES WYETH

SUPPLIED: Vacuum-packed tins of 48 troches.

Wyeth INCORPORATED, PHILADELPHIA 2, PA.

why Myocardone

is now the preferred treatment for Cardiac Decompensation Angina Pectoris

- **MYOCARDONE**—a new unique derivative of heart muscle—improves circulatory efficiency through potent cardiotonic and coronary vasodilator action.
- **MYOCARDONE** reduces or eliminates the need for nitrites in angina pectoris.
- **MYOCARDONE** has the added advantage of being virtually free from any untoward reactions. It is safe even when maximal dosage is administered for long periods.

The safety and efficacy of MYOCARDONE are proved by seven years of experimental and clinical research. For safer more dependable treatment of the cardiac patient specify MYOCARDONE. Available at your prescription pharmacy.

Literature on request

MYOCARDONE 1½ gr. tablets are supplied in bottles of 100. Suggested dosage—2 or 3 tablets T.I.D.

Chemico LABORATORIES, INC.
Indianapolis, Indiana

No activity pause at her menopause

Your patient may continue her normal activities even to the extent of keeping pace with her daughter. She will be greatly encouraged, especially when the effectiveness of therapy measures up to expectations. In estrogen therapy an especially useful product . . . . . is:

BENZESTROL

2,4 (p-hydroxyphenyl) –3– ethyl hexane

"Liver function tests, blood studies and urine examinations showed no toxic effects of the synthetic substance BENZESTROL"*

Supplied:

Oral: *Benzestrol* Tablets
0.5 Mg., 1.0 Mg., 100's & 1000's, 2 Mg., 5 Mg. — 50's — 100's — 1000's.

***Benzestrol* Elixir:**
15 Mg. per fluid ounce, Pint Bottles.

Intramuscular: *Benzestrol* Solution in Oil; Aqueous Suspension with 5% Benzyl Alcohol 5.0 Mg. per cc. 10cc Vials.

Local: *Benzestrol* Vaginal Tablets
0.5 Mg. 100's.

AVERAGE DOSE: Menopause — 2 to 3 Mg. daily orally or ½ to 1cc parenterally every 5 days.

Professional Samples and Literature upon Request

NOTE:

Frequently, medication other than estrogens may be required during the menopause. Pleasant tasting Elixir Benzestrol is compatible with many substances.

***Reference: MacBryde, C. M., et. al., *A New Synthetic Estrogen*, J.A.M.A., 123: 261: 264-(10-2) 43.**

Schieffelin & Co. **20 Cooper Square, New York 3, N. Y.**

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September, 1951

Metandren Linguets are specially prepared to permit efficient absorption through the mucosa of the mouth. Oral absorption completely avoids initial hepatic inactivation of the hormone. Therefore, the methyltestosterone is at least twice as effective as it is when swallowed.

When similarly administered, Metandren Linguets (methyltestosterone) were found to be "approximately twice as potent per milligram as unesterified testosterone, which in turn was approximately twice as potent as testosterone propionate."*

"Since the introduction of Metandren Linguets, a contribution of Ciba research, their proved economy, potency and convenience have gained for them extensive use as an established administration form for androgens.

Issued: Linguets, 5 mg. (white), and 10 mg. (yellow), scored.

*Lacassie, H. P. and Gordan, G. S.: J. Clin. Endocrinol. 10:249, 1950.

Ciba PHARMACEUTICAL PRODUCTS, INC., SUMMIT, N. J.

METANDREN LINGUETS